UNIVERSITÉ TOULOUSE III – Paul SABATIER
FACULTÉS DE MEDECINE

Année 2021 2021 TOU3 1587

THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
MÉDECINE SPÉCIALISÉE CLINIQUE

Présentée et soutenue publiquement
par

Maxime BENEYTO

Le 9 juillet 2021

PRÉDICTION DES ARYTHMIES VENTRICULAIRES PAR L'ANALYSE DE PHASE EN VENTRICULOGRAPHIE ISOTOPIQUE

Directeur de thèse : Pr Philippe MAURY

JURY :

Monsieur le Professeur Michel GALINIER	**Président**
Monsieur le Professeur Philippe MAURY	**Assesseur**
Monsieur le Professeur Olivier LAIREZ	**Assesseur**
Madame le Docteur Anne ROLLIN	**Assesseur**

TABLEAU du PERSONNEL HU
des Facultés de Médecine de l'Université Paul Sabatier
au 1er septembre 2020

Professeurs Honoraires

Doyen Honoraire	M. CHAP Hugues
Doyen Honoraire	M. GUIRAUD-CHAUMEIL Bernard
Doyen Honoraire	M. LAZORTHES Yves
Doyen Honoraire	M. PUEL Pierre
Doyen Honoraire	M. ROUGE Daniel
Doyen Honoraire	M. VINEL Jean-Pierre
Professeur Honoraire	M. ABBAL Michel
Professeur Honoraire	M. ADER Jean-Louis
Professeur Honoraire	M. ADOUE Daniel
Professeur Honoraire	M. ARBUS Louis
Professeur Honoraire	M. ARLET Jacques
Professeur Honoraire	M. ARLET Philippe
Professeur Honoraire	M. ARLET-SUAU Elisabeth
Professeur Honoraire	M. ARNE Jean-Louis
Professeur Honoraire	M. BARRET André
Professeur Honoraire	M. BARTHE Philippe
Professeur Honoraire	M. BAYARD Francis
Professeur Honoraire	M. BOCCALON Henri
Professeur Honoraire	M. BONAFÉ Jean-Louis
Professeur Honoraire	M. BONEU Bernard
Professeur Honoraire	M. BONNEVIALLE Paul
Professeur Honoraire	M. BOUNHOURE Jean-Paul
Professeur Honoraire	M. BOUTAULT Franck
Professeur Honoraire Associé	M. BROS Bernard
Professeur Honoraire	M. BUGAT Roland
Professeur Honoraire	M. CAHUZAC Jean-Philippe
Professeur Honoraire	M. CARATERO Claude
Professeur Honoraire	M. CARLES Pierre
Professeur Honoraire	M. CARRIERE Jean-Paul
Professeur Honoraire	M. CARTON Michel
Professeur Honoraire	M. CATHALA Bernard
Professeur Honoraire	M. CHABANON Gérard
Professeur Honoraire	M. CHAMONTIN Bernard
Professeur Honoraire	M. CHAP Hugues
Professeur Honoraire	M. CHAVOIN Jean-Pierre
Professeur Honoraire	M. CLANET Michel
Professeur Honoraire	M. CONTE Jean
Professeur Honoraire	M. COSTAGLIOLA Michel
Professeur Honoraire	M. COTONAT Jean
Professeur Honoraire	M. DABERNAT Henri
Professeur Honoraire	M. DAHAN Marcel
Professeur Honoraire	M. DALOUS Antoine
Professeur Honoraire	M. DALY-SCHVEITZER Nicolas
Professeur Honoraire	M. DAVID Jean-Frédéric
Professeur Honoraire	M. DELSOL Georges
Professeur Honoraire	Mme DELISLE Marie-Bernadette
Professeur Honoraire	Mme DIDIER Jacqueline
Professeur Honoraire	M. DUCOS Jean
Professeur Honoraire	M. DUFFAUT Michel
Professeur Honoraire	M. DUPRE M.
Professeur Honoraire	M. DURAND Dominique
Professeur Honoraire associé	M. DUTAU Guy
Professeur Honoraire	M. ESCANDE Michel
Professeur Honoraire	M. ESCHAPASSE Henri
Professeur Honoraire	M. ESCOURROU Jean
Professeur Honoraire	M. ESQUERRE J.P.
Professeur Honoraire	M. FABIÉ Michel
Professeur Honoraire	M. FABRE Jean
Professeur Honoraire	M. FOURNIAL Gérard
Professeur Honoraire	M. FOURNIE Bernard
Professeur Honoraire	M. FOURTANIER Gilles
Professeur Honoraire	M. FRAYSSE Bernard
Professeur Honoraire	M. FREXINOS Jacques
Professeur Honoraire	Mme GENESTAL Michèle
Professeur Honoraire	M. GERAUD Gilles
Professeur Honoraire	M. GHISOLFI Jacques
Professeur Honoraire	M. GLOCK Yves
Professeur Honoraire	M. GOUZI Jean-Louis
Professeur Honoraire	M. GRAND Alain
Professeur Honoraire	M. GUIRAUD CHAUMEIL Bernard
Professeur Honoraire	M. HOFF Jean
Professeur Honoraire	M. JOFFRE Francis
Professeur Honoraire	M. LACOMME Yves
Professeur Honoraire	M. LAGARRIGUE Jacques
Professeur Honoraire	M. LANG Thierry
Professeur Honoraire	Mme LARENG Marie-Blanche
Professeur Honoraire	M. LAURENT Guy
Professeur Honoraire	M. LAZORTHES Franck
Professeur Honoraire	M. LAZORTHES Yves
Professeur Honoraire	M. LEOPHONTE Paul
Professeur Honoraire	M. MAGNAVAL Jean-François
Professeur Honoraire	M. MANELFE Claude
Professeur Honoraire	M. MANSAT Michel
Professeur Honoraire	M. MASSIP Patrice
Professeur Honoraire	Mme MARTY Nicole
Professeur Honoraire	M. MAZIERES Bernard
Professeur Honoraire	M. MONROZIES Xavier
Professeur Honoraire	M. MOSCOVICI Jacques
Professeur Honoraire	M. MURAT
Professeur Honoraire associé	M. NICODEME Robert
Professeur Honoraire	M. OLIVES Jean-Pierre
Professeur Honoraire	M. PASCAL Jean-Pierre
Professeur Honoraire	M. PESSEY Jean-Jacques
Professeur Honoraire	M. PLANTE Pierre
Professeur Honoraire	M. PONTONNIER Georges
Professeur Honoraire	M. POURRAT Jacques
Professeur Honoraire	M. PRADERE Bernard
Professeur Honoraire	M. PRIS Jacques
Professeur Honoraire	Mme PUEL Jacqueline
Professeur Honoraire	M. PUEL Pierre
Professeur Honoraire	M. PUJOL Michel
Professeur Honoraire	M. QUERLEU Denis
Professeur Honoraire	M. RAILHAC Jean-Jacques
Professeur Honoraire	M. REGIS Henri
Professeur Honoraire	M. REGNIER Claude
Professeur Honoraire	M. REME Jean-Michel
Professeur Honoraire	M. RISCHMANN Pascal
Professeur Honoraire	M. RIVIERE Daniel
Professeur Honoraire	M. ROCHE Henri
Professeur Honoraire	M. ROCHICCIOLI Pierre
Professeur Honoraire	M. ROLLAND Michel
Professeur Honoraire	M. ROQUE-LATRILLE Christian
Professeur Honoraire	M. RUMEAU Jean-Louis
Professeur Honoraire	M. SALVADOR Michel
Professeur Honoraire	M. SALVAYRE Robert
Professeur Honoraire	M. SARRAMON Jean-Pierre
Professeur Honoraire	M. SIMON Jacques
Professeur Honoraire	M. SUC Jean-Michel
Professeur Honoraire	M. THOUVENOT Jean-Paul
Professeur Honoraire	M. TREMOULET Michel
Professeur Honoraire	M. VALDIGUIE Pierre
Professeur Honoraire	M. VAYSSE Philippe
Professeur Honoraire	M. VIRENQUE Christian
Professeur Honoraire	M. VOIGT Jean-Jacques

Professeurs Emérites

Professeur ADER Jean-Louis	Professeur SALVAYRE Robert
Professeur ALBAREDE Jean-Louis	Professeur SARRAMON Jean-Pierre
Professeur ARBUS Louis	Professeur SIMON Jacques
Professeur ARLET Philippe	
Professeur ARLET-SUAU Elisabeth	
Professeur BOCCALON Henri	
Professeur BOUTAULT Franck	
Professeur BONEU Bernard	
Professeur CARATERO Claude	
Professeur CHAMONTIN Bernard	
Professeur CHAP Hugues	
Professeur CONTÉ Jean	
Professeur COSTAGLIOLA Michel	
Professeur DABERNAT Henri	
Professeur FRAYSSE Bernard	
Professeur DELISLE Marie-Bernadette	
Professeur GUIRAUD-CHAUMEIL Bernard	
Professeur GRAND Alain	
Professeur JOFFRE Francis	
Professeur LAGARRIGUE Jacques	
Professeur LANG Thierry	
Professeur LAURENT Guy	
Professeur LAZORTHES Yves	
Professeur MAGNAVAL Jean-François	
Professeur MANELFE Claude	
Professeur MASSIP Patrice	
Professeur MAZIERES Bernard	
Professeur MOSCOVICI Jacques	
Professeur MURAT	
Professeur RISCHMANN Pascal	
Professeur RIVIERE Daniel	
Professeur ROQUES-LATRILLE Christian	

FACULTE DE MEDECINE TOULOUSE-PURPAN

37 allées Jules Guesde - 31062 TOULOUSE Cedex — **Doyen : D. CARRIE**

P.U. - P.H.
Classe Exceptionnelle et 1ère classe

M. AMAR Jacques	Thérapeutique
M. ATTAL Michel (C.E)	Hématologie
M. AVET-LOISEAU Hervé	Hématologie, transfusion
Mme BEYNE-RAUZY Odile	Médecine Interne
M. BIRMES Philippe	Psychiatrie
M. BLANCHER Antoine (C.E)	Immunologie (option Biologique)
M. BOSSAVY Jean-Pierre (C.E)	Chirurgie Vasculaire
M. BRASSAT David	Neurologie
M. BROUCHET Laurent	Chirurgie thoracique et cardio-vascul
M. BROUSSET Pierre (C.E)	Anatomie pathologique
M. BUREAU Christophe	Hépato-Gastro-Entérologie
M. CALVAS Patrick (C.E)	Génétique
M. CARRERE Nicolas	Chirurgie Générale
M. CARRIE Didier (C.E)	Cardiologie
M. CHAIX Yves	Pédiatrie
Mme CHARPENTIER Sandrine	Médecine d'urgence
M. CHAUVEAU Dominique	Néphrologie
M. CHOLLET François (C.E)	Neurologie
M. DE BOISSEZON Xavier	Médecine Physique et Réadapt Fonct.
M. DEGUINE Olivier (C.E)	Oto-rhino-laryngologie
M. DUCOMMUN Bernard	Cancérologie
M. FERRIERES Jean (C.E)	Epidémiologie, Santé Publique
M. FOURCADE Olivier	Anesthésiologie
M. FOURNIÉ Pierre	Ophtalmologie
M. GAME Xavier	Urologie
M. GEERAERTS Thomas	Anesthésiologie et réanimation
M. IZOPET Jacques (C.E)	Bactériologie-Virologie
Mme LAMANT Laurence (C.E)	Anatomie Pathologique
M. LANGIN Dominique (C.E)	Nutrition
M. LAUQUE Dominique (C.E)	Médecine d'Urgence
M. LAUWERS Frédéric	Chirurgie maxillo-faciale
M. LEOBON Bertrand	Chirurgie Thoracique et Cardiaque
M. LIBLAU Roland (C.E)	Immunologie
M. MALAVAUD Bernard	Urologie
M. MANSAT Pierre	Chirurgie Orthopédique
M. MARCHOU Bruno	Maladies Infectieuses
M. MAS Emmanuel	Pédiatrie
M. MAZIERES Julien	Pneumologie
M. MOLINIER Laurent	Epidémiologie, Santé Publique
M. MONTASTRUC Jean-Louis (C.E)	Pharmacologie
Mme MOYAL Elisabeth (C.E)	Cancérologie
Mme NOURHASHEMI Fatemeh (C.E)	Gériatrie
M. OSWALD Eric (C.E)	Bactériologie-Virologie
M. PARANT Olivier	Gynécologie Obstétrique
M. PARIENTE Jérémie	Neurologie
M. PARINAUD Jean (C.E)	Biol. Du Dévelop. et de la Reprod.
M. PAUL Carle (C.E)	Dermatologie
M. PAYOUX Pierre	Biophysique
M. PAYRASTRE Bernard (C.E)	Hématologie
M. PERON Jean-Marie	Hépato-Gastro-Entérologie
M. PERRET Bertrand (C.E)	Biochimie
M. RASCOL Olivier (C.E)	Pharmacologie
M. RECHER Christian(C.E)	Hématologie
M. RONCALLI Jérôme	Cardiologie
M. SALES DE GAUZY Jérôme (C.E)	Chirurgie Infantile
M. SALLES Jean-Pierre (C.E)	Pédiatrie
M. SANS Nicolas	Radiologie
Mme SELVES Janick	Anatomie et cytologie pathologiques
M. SERRE Guy (C.E)	Biologie Cellulaire
M. SOL Jean-Christophe	Neurochirurgie
M. TELMON Norbert (C.E)	Médecine Légale
M. VINEL Jean-Pierre (C.E)	Hépato-Gastro-Entérologie

P.U. Médecine générale

M. OUSTRIC Stéphane (C.E)

Professeur Associé de Médecine Générale

Mme IRI-DELAHAYE Motoko

P.U. - P.H.
2ème classe

Mme BONGARD Vanina	Epidémiologie
M. BONNEVIALLE Nicolas	Chirurgie orthopédique et traumatologique
Mme CASPER Charlotte	Pédiatrie
M. CAVAIGNAC Etienne	Chirurgie orthopédique et traumatologie
M. COGNARD Christophe	Neuroradiologie
M. LAIREZ Olivier	Biophysique et médecine nucléaire
M. LAROCHE Michel	Rhumatologie
M. LOPEZ Raphael	Anatomie
M. MARTIN-BLONDEL Guillaume	Maladies infectieuses, maladies tropicales
M. MARX Mathieu	Oto-rhino-laryngologie
M. OLIVOT Jean-Marc	Neurologie
M. PAGES Jean-Christophe	Biologie cellulaire
Mme PASQUET Marlène	Pédiatrie
M. PORTIER Guillaume	Chirurgie Digestive
Mme RUYSSEN-WITRAND Adeline	Rhumatologie
Mme SAVAGNER Frédérique	Biochimie et biologie moléculaire
M. SIZUN Jacques	Pédiatrie
Mme TREMOLLIERES Florence	Biologie du développement
Mme VAYSSE Charlotte	Cancérologie
Mme VEZZOSI Delphine	Endocrinologie

P.U. Médecine générale

M. MESTHÉ Pierre

Professeur Associé Médecine générale

M. ABITTEBOUL Yves

M. POUTRAIN Jean-Christophe

Professeur Associé en Bactériologie-Hygiène

Mme MALAVAUD Sandra

FACULTE DE MEDECINE TOULOUSE-RANGUEIL

133, route de Narbonne - 31062 TOULOUSE Cedex — **Doyen : E. SERRANO**

P.U. - P.H.
Classe Exceptionnelle et 1ère classe

M. ACAR Philippe	Pédiatrie
M. ACCADBLED Franck	Chirurgie Infantile
M. ALRIC Laurent (C.E)	Médecine Interne
Mme ANDRIEU Sandrine	Epidémiologie
M. ARBUS Christophe	Psychiatrie
M. ARNAL Jean-François	Physiologie
M. BERRY Antoine	Parasitologie
Mme BERRY Isabelle (C.E)	Biophysique
M. BONNEVILLE Fabrice	Radiologie
M. BUJAN Louis (C. E)	Urologie-Andrologie
Mme BURA-RIVIERE Alessandra	Médecine Vasculaire
M. BUSCAIL Louis (C.E)	Hépato-Gastro-Entérologie
M. CANTAGREL Alain (C.E)	Rhumatologie
M. CARON Philippe (C.E)	Endocrinologie
M. CHAUFOUR Xavier	Chirurgie Vasculaire
M. CHAYNES Patrick	Anatomie
M. CHIRON Philippe (C.E)	Chirurgie Orthopédique et Traumatologie
M. CONSTANTIN Arnaud	Rhumatologie
M. COURBON Frédéric	Biophysique
Mme COURTADE SAIDI Monique	Histologie Embryologie
M. DAMBRIN Camille	Chirurgie Thoracique et Cardiovasculaire
M. DELABESSE Eric	Hématologie
M. DELOBEL Pierre	Maladies Infectieuses
M. DELORD Jean-Pierre (C.E)	Cancérologie
M. DIDIER Alain (C.E)	Pneumologie
Mme DULY-BOUHANICK Béatrice (C.E)	Thérapeutique
M. ELBAZ Meyer	Cardiologie
M. GALINIER Michel (C.E)	Cardiologie
Mme GOMEZ-BROUCHET Anne-Muriel	Anatomie Pathologique
M. GOURDY Pierre	Endocrinologie
M. GROLLEAU RAOUX Jean-Louis (C.E)	Chirurgie plastique
Mme GUIMBAUD Rosine	Cancérologie
Mme HANAIRE Hélène (C.E)	Endocrinologie
M. HUYGHE Eric	Urologie
M. KAMAR Nassim (C.E)	Néphrologie
M. LARRUE Vincent	Neurologie
M. LEVADE Thierry (C.E)	Biochimie
M. MALECAZE François (C.E)	Ophtalmologie
M. MARQUE Philippe (C.E)	Médecine Physique et Réadaptation
M. MAURY Jean-Philippe	Cardiologie
Mme MAZEREEUW Juliette	Dermatologie
M. MINVILLE Vincent	Anesthésiologie Réanimation
M. MUSCARI Fabrice	Chirurgie Digestive
M. RAYNAUD Jean-Philippe (C.E)	Psychiatrie Infantile
M. RITZ Patrick (C.E)	Nutrition
M. ROLLAND Yves (C.E)	Gériatrie
M. ROUGE Daniel (C.E)	Médecine Légale
M. ROUSSEAU Hervé (C.E)	Radiologie
M. ROUX Franck-Emmanuel	Neurochirurgie
M. SAILLER Laurent (C.E)	Médecine Interne
M. SCHMITT Laurent (C.E)	Psychiatrie
M. SENARD Jean-Michel (C.E)	Pharmacologie
M. SERRANO Elie (C.E)	Oto-rhino-laryngologie
M. SOULAT Jean-Marc	Médecine du Travail
M. SOULIE Michel (C.E)	Urologie
M. SUC Bertrand	Chirurgie Digestive
Mme TAUBER Marie-Thérèse (C.E)	Pédiatrie
Mme URO-COSTE Emmanuelle (C.E)	Anatomie Pathologique
M. VAYSSIERE Christophe	Gynécologie Obstétrique
M. VELLAS Bruno (C.E)	Gériatrie

Professeur Associé de Médecine Générale

M. STILLMUNKES André

P.U. - P.H.
2ème classe

M. ABBO Olivier	Chirurgie infantile
M. AUSSEIL Jérôme	Biochimie et biologie moléculaire
M. BOUNES Vincent	Médecine d'urgence
Mme BOURNET Barbara	Gastro-entérologie
M. CHAPUT Benoit	Chirurgie plastique et des brûlés
Mme DALENC Florence	Cancérologie
M. DE BONNECAZE Guillaume	Oto-rhino-laryngologie
M. DECRAMER Stéphane	Pédiatrie
M. FAGUER Stanislas	Néphrologie
Mme FARUCH BILFELD Marie	Radiologie et imagerie médicale
M. FRANCHITTO Nicolas	Addictologie
Mme GARDETTE Virginie	Epidémiologie
M. GARRIDO-STÖWHAS Ignacio	Chirurgie Plastique
M. GUILLEMINAULT Laurent	Pneumologie
Mme LAPRIE Anne	Radiothérapie
Mme LAURENT Camille	Anatomie Pathologique
M. LE CAIGNEC Cédric	Génétique
M. LEANDRI Roger	Biologie du dével. et de la reproduction
M. MARCHEIX Bertrand	Chirurgie thoracique et cardiovasculaire
M. MEYER Nicolas	Dermatologie
M. PUGNET Grégory	Médecine interne
M. REINA Nicolas	Chirurgie orthopédique et traumatologique
M. SILVA SIFONTES Stein	Réanimation
M. SOLER Vincent	Ophtalmologie
Mme SOMMET Agnès	Pharmacologie
Mme SOTO-MARTIN Maria-Eugénia	Gériatrie et biologie du vieillissement
M. TACK Ivan	Physiologie
M. VERGEZ Sébastien	Oto-rhino-laryngologie
M. YSEBAERT Loic	Hématologie

P.U. Médecine générale

Mme ROUGE-BUGAT Marie-Eve

Professeur Associé de Médecine Générale

M. BOYER Pierre

FACULTE DE MEDECINE TOULOUSE-PURPAN

37, allées Jules Guesde – 31062 Toulouse Cedex

M.C.U. - P.H.

M. APOIL Pol Andre	Immunologie
Mme ARNAUD Catherine	Epidémiologie
Mme AUSSEIL-TRUDEL Stéphanie	Biochimie
Mme BELLIERES-FABRE Julie	Néphrologie
Mme BERTOLI Sarah	Hématologie, transfusion
M. BIETH Eric	Génétique
Mme CASPAR BAUGUIL Sylvie	Nutrition
Mme CASSAGNE Myriam	Ophtalmologie
Mme CASSAING Sophie	Parasitologie
Mme CHANTALAT Elodie	Anatomie
M. CONGY Nicolas	Immunologie
Mme COURBON Christine	Pharmacologie
M. CUROT Jonathan	Neurologie
Mme DAMASE Christine	Pharmacologie
Mme de GLISEZENSKY Isabelle	Physiologie
M. DUBOIS Damien	Bactériologie Virologie Hygiène
Mme FILLAUX Judith	Parasitologie
M. GANTET Pierre	Biophysique
Mme GENNERO Isabelle	Biochimie
Mme GENOUX Annelise	Biochimie et biologie moléculaire
M. HAMDI Safouane	Biochimie
Mme HITZEL Anne	Biophysique
M. IRIART Xavier	Parasitologie et mycologie
Mme JONCA Nathalie	Biologie cellulaire
M. KIRZIN Sylvain	Chirurgie générale
Mme LAPEYRE-MESTRE Maryse	Pharmacologie
M. LHERMUSIER Thibault	Cardiologie
M. LHOMME Sébastien	Bactériologie-virologie
Mme MASSIP Clémence	Bactériologie-virologie
Mme MONTASTIER Emilie	Nutrition
Mme MOREAU Marion	Physiologie
Mme NOGUEIRA M.L.	Biologie Cellulaire
Mme PERROT Aurore	Hématologie
M. PILLARD Fabien	Physiologie
Mme PUISSANT Bénédicte	Immunologie
Mme RAYMOND Stéphanie	Bactériologie Virologie Hygiène
Mme SABOURDY Frédérique	Biochimie
Mme SAUNE Karine	Bactériologie Virologie
M. TAFANI Jean-André	Biophysique
M. TREINER Emmanuel	Immunologie

M.C.U. Médecine générale

M. BRILLAC Thierry

Mme DUPOUY Julie

M.C.A. Médecine Générale

Mme FREYENS Anne

M. CHICOULAA Bruno

Mme PUECH Marielle

FACULTE DE MEDECINE TOULOUSE- RANGUEIL

133, route de Narbonne - 31062 TOULOUSE cedex

M.C.U. - P.H

Mme ABRAVANEL Florence	Bactériologie Virologie Hygiène
Mme BASSET Céline	Cytologie et histologie
Mme BREHIN Camille	Pneumologie
Mme CAMARE Caroline	Biochimie et biologie moléculaire
M. CAMBUS Jean-Pierre	Hématologie
Mme CANTERO Anne-Valérie	Biochimie
Mme CARFAGNA Luana	Pédiatrie
Mme CASSOL Emmanuelle	Biophysique
M. CHASSAING Nicolas	Génétique
M. CLAVEL Cyril	Biologie Cellulaire
Mme COLOMBAT Magali	Anatomie et cytologie pathologiques
Mme CORRE Jill	Hématologie
M. DEDOUIT Fabrice	Médecine Légale
M. DEGBOE Yannick	Rhumatologie
M. DELPLA Pierre-André	Médecine Légale
M. DESPAS Fabien	Pharmacologie
M. EDOUARD Thomas	Pédiatrie
Mme ESQUIROL Yolande	Médecine du travail
Mme EVRARD Solène	Histologie, embryologie et cytologie
Mme FLOCH Pauline	Bactériologie-Virologie
Mme GALINIER Anne	Nutrition
Mme GALLINI Adeline	Epidémiologie
M. GASQ David	Physiologie
M. GATIMEL Nicolas	Médecine de la reproduction
Mme GRARE Marion	Bactériologie Virologie Hygiène
M. GUERBY Paul	Gynécologie-Obstétrique
M. GUIBERT Nicolas	Pneumologie
Mme GUILBEAU-FRUGIER Céline	Anatomie Pathologique
Mme GUYONNET Sophie	Nutrition
M. HERIN Fabrice	Médecine et santé au travail
Mme INGUENEAU Cécile	Biochimie
M. LEPAGE Benoit	Biostatistiques et Informatique médicale
Mme MAUPAS SCHWALM Françoise	Biochimie
M. MOULIS Guillaume	Médecine interne
Mme NASR Nathalie	Neurologie
Mme QUELVEN Isabelle	Biophysique et médecine nucléaire
M. RIMAILHO Jacques	Anatomie et Chirurgie Générale
Mme SIEGFRIED Aurore	Anatomie et cytologie pathologiques
Mme VALLET Marion	Physiologie
M. VERGEZ François	Hématologie
Mme VIJA Lavinia	Biophysique et médecine nucléaire
M. YRONDI Antoine	Psychiatrie d'adultes

M.C.U. Médecine générale

M. BISMUTH Michel

M. ESCOURROU Emile

M.C.A. Médecine Générale

M. BIREBENT Jordan

Mme BOURGEOIS Odile

Mme BOUSSIER Nathalie

Mme LATROUS Leila

REMERCIEMENTS

Au Professeur Philippe MAURY,

Ta passion et ton énergie forcent l'admiration. C'est un honneur que te travailler à tes côtés et suivre ton enseignement.

Au Professeur Olivier LAIREZ,

Tu as été un des premiers à m'accorder ta confiance ; c'est grâce à toi que j'ai pu me lancer dans la recherche clinique. Tu t'es dévoué à organiser la formation de mes co-internes et de moi-même et je t'en suis particulièrement reconnaissant.

Au Professeur Michel GALINIER,

Dès le premier jour, vous avez assuré l'aiguillage de mon internat et avez permis que j'en sois là aujourd'hui. Il était naturel que vous fassiez partie de mon jury.

Au Docteur Anne ROLLIN,

Merci d'avoir accepté d'être présente à ma soutenance de thèse. Tu es un modèle de réussite pour moi et j'espère que les années me permettront de te ressembler.

DEDICACES

A Anna, mon amour, mon guide, mon icône, ma joie et mon bonheur.

A mes parents, à ma sœur, dont le soutien indéfectible m'a permis de tout entreprendre et m'a permis de réussir.

A mes co-internes Arthur G, Arthur P, Clarisse, Henri, Laetitia, Laure et Laurence avec qui j'ai traversé l'internat. Que notre amitié ne s'estompe jamais avec le temps. A ceux qui m'ont montré le chemin : Clément, Sophie, Maëva, Clémence, Lucas, Romain, Daniel, Alex, Hugo, Grégoire, Gaëtan, Damien, Jérémy B, Jérémy L, Stéphanie B, Robin, Fabien, Aenora, Virginie, Hubert, Stéphanie C, Jérôme, Guillaume, Kévin, Valérie, Franck, Adrien, Slimane, Nicolas, Antoine. Et à ceux qui m'ont suivi Thibaut, Nathan, Jean-Baptiste, Anthony R, Anthony T, Kévin, Déborah, Marie, Miloud, Marine, Laurine, Maxime, Paul G, Paul V, Matthieu, Mickaël, Hélène, Gabriel, François et ceux que je n'ai pas encore rencontré.

A mes Maîtres Pr Carrié, Camelia, Maryse, Wiem, Farès, Romain, Clémence, Frédéric, Stéphanie, Pr Elbaz, Marine, Francisco, Thibault, Nicolas, Thomas C, Elisabeth, Florence, Pr Amar, Thomas M, Eve, Yoan, Pierre, Delphine, Guillaume, Clément, Caroline, Guillaume, Pascale, Hélène, Julien, Paul, Bénédicte, Julia, Pauline, Pr Roncalli, Benjamin, Quentin, Alexandre, Pierre.

Au personnel paramédical, sans qui nos connaissances n'auraient pas plus d'utilité que de belles paroles.

A mes externes, ceux qui ont encore une question à poser, ceux qui n'osent pas partir et ceux qui ont toujours une bonne raison pour partir tôt.

To Brice, Dyani, Amy, Ed, Xiaoyuan, Kaz, Nima, Sajjad, Tony and all the members of the « BOL Lab ». You gave me one of my best memories, I have not given up on seeing you again!

TABLE DES MATIERES

List of abbreviations

GLS, global longitudinal strain;

HTx, heart transplantation;

ICD, implantable cardioverter-defibrillator;

LV, left ventricle;

LVEF, left ventricular ejection fraction;

PSD, left ventricle phase standard deviation;

RNV, radionuclide ventriculography;

TPSSD, time-to-peak strain standard deviation;

TTE, transthoracic echocardiography;

VA, ventricular arrhythmia.

Introduction

Prediction of potentially lethal ventricular arrhythmias (VAs) is a still unmet need in cardiology that could both save lives of at-risk patients and avoid potentially harmful interventions in patients that are not at-risk.

The most used parameter to assess this risk is left ventricular ejection fraction (LVEF). Though, that parameter is well known to suffer several limitations and that numerous VAs happen in patients for whom the <35% cutoff is not reached.[1]

With the technological advances in transthoracic echocardiography (TTE), new tools have been developed and validated to further predict the risk of VA. Notably, speckle tracking allows the assessment of mechanical dispersion. This parameter, defined as the standard deviation of mean time from R wave on electrocardiogram to peak longitudinal strain (TPSSD) across the 17 left ventricular (LV) segments, is a marker of electromechanical heterogeneity. This heterogeneity may reflect the existence of late excitable myocardial segments allowing reentry and thus VAs. This association is independent of LVEF and LV global longitudinal strain (GLS). The most evidence was gathered in post-myocardial infarction[2–5] and non-ischemic cardiomyopathy,[2,6] but also in hypertrophic cardiomyopathy patients.[7] A recent meta-analysis[2] demonstrated that a >60 ms cutoff displayed an area under curve of about 75% for VA risk prediction, making it a promising tool to assist in deciding the implantation of a cardioverter-defibrillator (ICD). The main caveat—as for all TTE measurement—is poor ultrasonographic window that precludes the use of speckle tracking. Additionally, despite acceptable measurement reproducibility, cut-off values are subject to wide variation from one study to another.

In daily practice, gated tomographic equilibrium blood pool radionuclide ventriculography (RNV) is commonly used to confirm TTE measurements or overcome echogenicity limitations. In particular, it allows volumes and ejection fraction evaluation for both ventricles without geometric assumption. Additionally, in phase image analysis, RNV can study LV mechanical dispersion similarly to speckle tracking with TTE. Considering that it is simple to perform and exhibits excellent reproducibility, it has great potential and could be easier to implement in practice than mechanical dispersion measured by TTE.

From a pathophysiological standpoint, some part of mechanical dispersion is expected to be a macroscopic mechanical reflection of electrophysiological dispersion, for example caused by nonuniform anisotropy of the myocardium and slow delayed local conduction. As

explained earlier both properties play a role in myocardial susceptibility to arrhythmias. This is supported by the recent study of Trivedi et al.[8] which demonstrated a correlation between strain-derived mechanical dispersion and scar extent on invasive electroanatomic mapping in ischemic cardiomyopathy.

Radionuclide LV mechanical dispersion has been studied proficiently to predict targets and effectiveness of resynchronization therapy.[9–11] To the best of our knowledge, only two studies hitherto used phase image analysis to evaluate the risk of VA occurrence.[12,13] Both found no association of PSD with the event at hand. Though, one used planar acquisition only, which we suspect to be less accurate than tomographic acquisitions; the other studied idiopathic ventricular tachycardia in children, hence morphologically normal hearts that are unlikely to display increased mechanical dispersion.

In the present retrospective single-centered cohort study, we intended to assess the ability of LV mechanical dispersion, as measured by phase image analysis of tomographic radionuclide ventriculography, to predict the risk of VA occurrence in an unselected population of patients.

Methods

Study design

We conducted a monocentric retrospective cohort study.

Study population

Were eligible all patients who underwent an RNV from Jan 1st, 2015 to Dec 31st, 2019 in the Nuclear Medicine department of Toulouse University Hospital. When no follow-up data was available after image acquisition, patients were excluded.

Image acquisition and data analysis

ECG-gated images were acquired in a 64 × 64 rotating matrix formats at 16 frames per cycle. Acquisition depth ranged from 29 to 54 slices. Voxel edge lengths ranged from 4.92 mm to 6.59 mm. Acquisitions were performed with a Symbia T6 gamma camera (Siemens, Munich, Germany) or a D-SPECT cadmium-zinc-telluride gamma camera (Spectrum Dynamics Medical, Sarasota, FL, USA).

The isotopic tracer was ^{99m}Tc-pertechnetate administered intravenously 30 minutes after the injection of 10 – 20 mg/kg of stannous pyrophosphate; image acquisition was performed subsequently.

The first harmonic Fourier transform yielded phase angle on a composite cardiac cycle represented as a sinusoid beginning at the peak of the R wave. Mechanical activation delay was then computed using the average cycle length during the RNV. We used QBS 2009 (Cedars-Sinai, Los Angeles, CA, USA) for automated image processing (Figure 1).

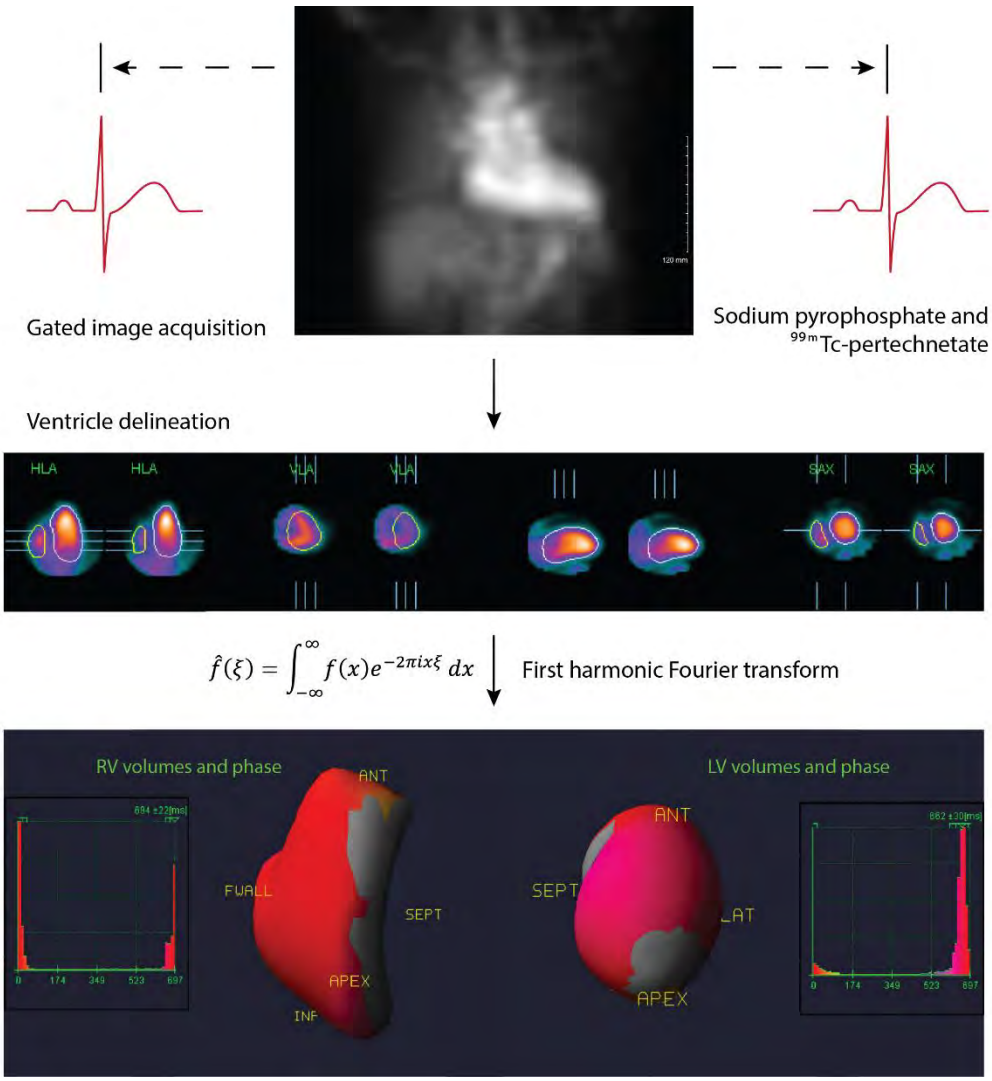


Figure 1. Schematic representation of nuclear image acquisition and processing.

Top: Gated raw RNV acquisition, anteroposterior view. Middle: Left and right ventricular delineation on planar projections (from left to right: four-chamber, right ventricle long axis, left ventricle long axis, short axis). Bottom: three-dimensional rendering of right and left ventricles with phase histograms.

For 1) patients in which images consisted in planar-only acquisitions and 2) patients in whom image reconstruction failed or in whom the software consistently yielded aberrant results, another RNV performed during the study period and showing satisfactory quality could be used instead. Otherwise, these patients were excluded.

Heart chamber volumes were indexed to body surface area (computed with the Du Bois formula).

RNV-derived mechanical dispersion was defined as the standard deviation of LV phase across all 17 myocardial segments.[9] For better understandability, phase standard deviation (PSD) was expressed as a duration in milliseconds.

Whenever available, TTE loops were reviewed by a trained cardiologist to obtain longitudinal strain-derived mechanical dispersion. It was defined as the standard deviation of the time-to-peak strain (TPSSD) across all 17 myocardial segments. All TTEs were performed on General Electric ultrasound systems (General Electric, Boston, MA, USA) and TPSSD measurements were obtained with EchoPAC Software v202 (General Electric, Boston, MA, USA).

Endpoint

The primary endpoint was malignant VA events occurring after RNV. Malignant VA events were defined as sudden cardiac death (unexpected death within 1 hour of onset of cardiac manifestations in the absence of previous hemodynamic manifestations, death during sleep, or within 24 hours after the patient was last seen alive and apparently stable clinically), documented ventricular fibrillation, documented sustained ventricular tachycardia, and appropriate ICD therapy (anti-tachycardia pacing or shock delivered on episodes of ventricular tachycardia or ventricular fibrillation). Death and heart transplantation were also recorded as they represent competing risks for VA and censoring events. Events were collected retrospectively from the patients' medical records. Whenever recent clinical status was not available in our center's medical files, we reached out to the patients' general practitioner or cardiologist to complete follow-up data. In patients implanted with cardiac electronic devices, remote monitoring data were used to collect VA events. Diagnoses of appropriate ICD therapy were validated by a trained electrophysiologist in all cases.

Ethics

According to the French ethic and regulatory laws, retrospective studies based on the exploitation of usual care data do not require submission to an ethical committee but have to be covered by reference methodology of the French National Commission for Informatics

and Liberties (CNIL). After evaluation and validation by the data protection officer and according to the General Data Protection Regulation, this study was listed in the register of retrospective study of the Toulouse University Hospital (number RnIPH 2020-123) and covered by the MR-004 (CNIL number: 2206723 v 0).

Statistical analysis

With an expected event rate of 10% and a fixed risk alpha of 0.05, the size of our study granted an 80% power to detect a hazard ratio as low as 1.06 per 10 ms increase in PSD.

All statistical analyses were performed with R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous variables are presented as mean ± standard deviation when normally distributed or as median (quartiles) otherwise. Continuous variable differences were tested with Wilcoxon signed rank tests. Categorical variables are presented as counts (percentages).

Cox proportional hazard models were performed using the *survival* package version 3.2.11. The proportional hazard assumptions were assessed with Schoenfeld tests. Associations were reported as hazard ratios (HR) and their corresponding 95% confidence intervals (CI). Robust estimation was performed to avoid artificial population size inflation in case of occurrence of several events in one subject.

Kaplan-Meier curves allowed the estimation of the distribution of the time to event. A multi-state "clock forward" Markov proportional hazards model as described in Supplemental Figure 1 was used to take into account both competing risks and the ability of patients to experience consecutive events. We restricted our analysis to the first VA to occur after RNV for simplicity, even though iterative events are possible. For pathophysiological coherence, heart transplantation was defined as a right-censored absorbing state, with no transition possible to death. In patients with heart transplantation, follow-up was considered to end at the time of surgery.

Although erroneous, for simplicity, characteristics of the patient were assumed to be invariable over time.

Unadjusted cumulative incidence curves were calculated for the primary outcome stratified by tertiles, as well as for the composite outcome of first occurring VA, heart transplantation or death, for heart transplantation, and finally for death.

A prespecified subgroup analysis was performed in patients equipped with an ICD, in which follow-up is expected to be sturdier as all VAs ought to be recorded. The effect of gamma camera, previous VA and previous ventricular ablation on the ability of PSD to predict new VAs was assessed through an interaction term in the survival analysis. The association of established risk factors (age, sex, presence of wide QRS >120 ms, LVEF, LV GLS and TPSSD) and VAs was assessed in univariate survival analysis. Then, the association of PSD and VAs after adjustment for these risk factors was evaluated with multivariate survival analysis. Other usual markers of VA risk, such as MRI data, could not be added in analysis since not available in most patients.

Analyses involving both TTE and RNV data were weighted according to the temporal gap between these two exams.

Receiver-operating characteristics were computed with the *pROC* package version 1.17.0.1. The best performing cutoff for PSD was selected based on survival analysis (Supplemental material).

All tests were two-sided and p-values <0.05 were considered statistically significant.

No correction method for missing data was applied as they did not concern the primary analysis. Whenever missing data existed, their number was displayed, and they were removed from the statistical analysis.

References for statistical analysis can be found in Supplemental material.

Results

Participants

We identified 949 patients with qualifying exams over the study period. After excluding 12 subjects for insufficient baseline and follow-up data, our population totalized 937 patients. The detailed process is summarized in Figure 2.

Population characteristics

Clinical data

The "median patient" was an overweight 59 years-old male with an ischemic heart disease. Clinical characteristics of the population are provided in Table 1.

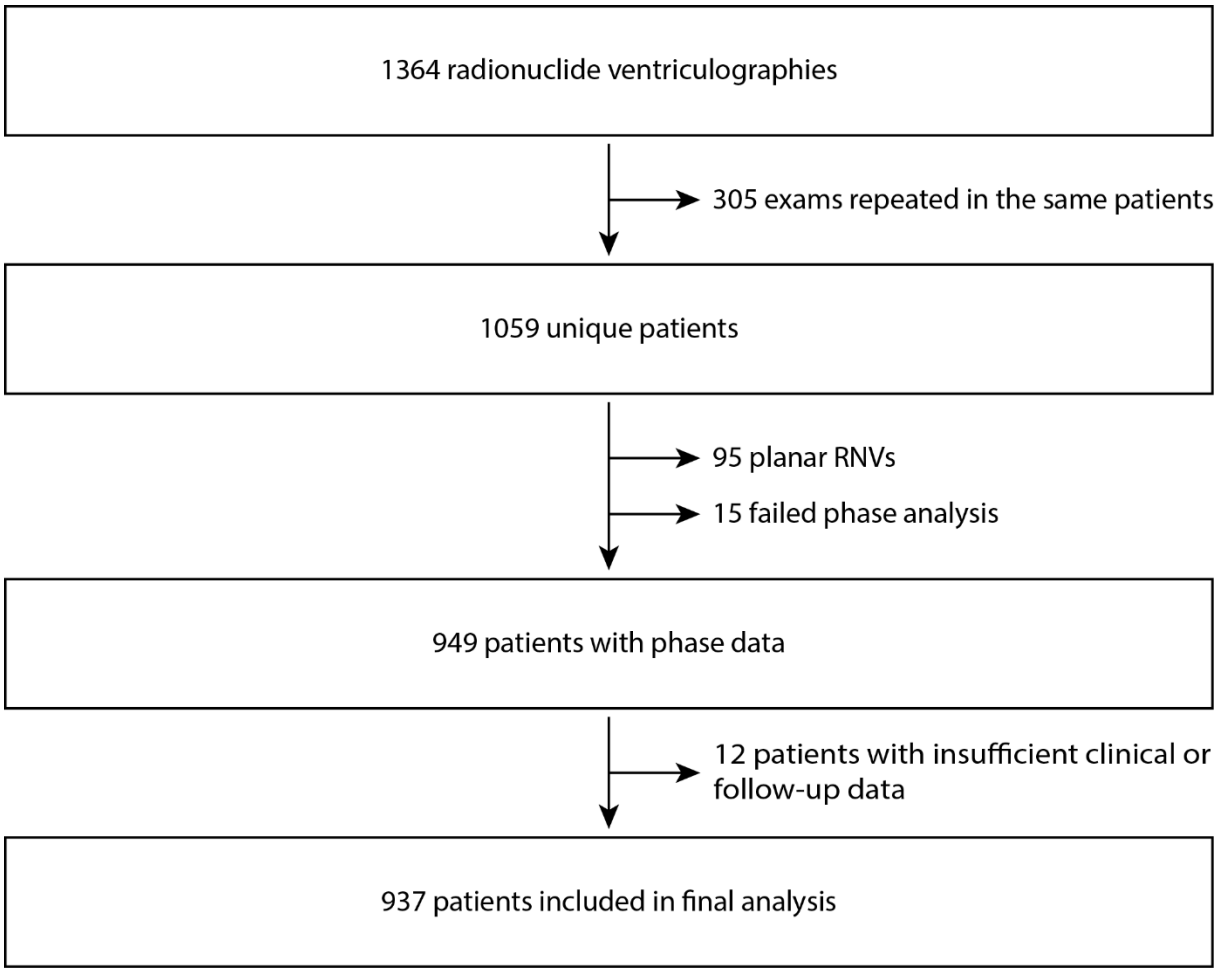


Figure 2. Flowchart diagram.

Reasons for failed phase analysis were: too irregular or too slow heart rate, not enough counts, extreme heart anatomy.

Baseline characteristics	**Study population (*N* = 937)**	**Missing**
Female sex, *n* (%)	243 (25.9)	0 (0)
Age (years)	59 (50 – 67)	0 (0)
BMI (kg/m²)	26.1 (23.0 – 29.7)	0 (0)
BSA (m²)	1.91 ± 0.23	0 (0)
NYHA class	2 (1 – 3)	50 (5.3)
Heart rate (bpm)	69 (60 – 78)	0 (0)
Main cardiomyopathy, *n* (%)		0 (0)
Ischemic	334 (35.6)	
Dilated non-ischemic	245 (26.1)	
Tachycardia-induced	20 (2.1)	
ARVC	52 (5.5)	
Channelopathy or idiopathic ventricular arrhythmias	40 (4.3)	
Valvular	76 (8.1)	
Infiltrative	12 (1.3)	
Post-hypertensive	6 (0.6)	
Hypertrophic (sarcomeric)	6 (0.6)	
Other	80 (8.5)	
None	66 (7.0)	
Medication use, *n* (%)		
AAD class Ic	6 (0.6)	3 (0.3)
Beta-blockers	576 (61.7)	3 (0.3)
AAD class III	184 (19.7)	5 (0.5)
AAD class IV	11 (1.2)	3 (0.3)
Ivabradine	65 (7.0)	3 (0.3)
ACEi or ARB	407 (43.6)	3 (0.3)
MRA	390 (41.8)	3 (0.3)

Neprilysin inhibitor	116 (12.4)	3 (0.3)
QRS duration >120 ms, *n* (%)	284 (31.2)	28 (3.0)
History of arrhythmia, *n* (%)		
Atrial fibrillation	296 (31.8)	5 (0.5)
Previous	179 (19.2)	
Ongoing	117 (12.6)	
Ventricular arrhythmia*	142 (15.3)	0 (0)
Previous VT ablation	52 (5.5)	0 (0)
Device therapy, *n* (%)		
Pacemaker	40 (4.2)	1 (0.1)
CRT	102 (10.9)	1 (0.1)
ICD	331 (35.4)	1 (0.1)
LVAD	32 (3.4)	0 (0.0)

Table 1. Population baseline characteristics.

*Previous ventricular arrhythmias had the same definition as ventricular arrhythmia events.

AAD, anti-arrhythmic drug (Vaughan-Williams' classification); ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARVC, arrhythmogenic right ventricular cardiomyopathy; bpm, beats per minute; BMI, body mass index; BSA, body surface area; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; VT, ventricular tachycardia.

Radionuclide ventriculography

The median radiation dose administered was 744 (733 – 757) MBq. Four hundred and twenty-five (45%) patients had a severely depressed LVEF ≤35%, with a median LVEF of 38% (23 – 59) and 427 (46%) had a dilated LV. Four hundred and ninety-eight (53%) patients had a depressed right ventricular ejection fraction <45%, with a median of 44% (35 – 53) and 427 (46%) had a dilated right ventricle. Median PSD was 43 (19 – 92) ms. PSD was significantly greater in RNVs performed with D-SPECT gamma camera (46 (24 – 88) ms), rather than with Symba T6 gamma camera (39 (16 – 93) ms, $p < 0.05$). Table 2 sums RNV results up.

Transthoracic echocardiography

Even though TTE was performed in 943 (97%) patients, only 659 (70%) of them had suitable exam quality to obtain TPSSD. With this imaging modality, 445 (51%) of patients had a severely depressed LVEF ≤35%, with a median LVEF of 36% (25 – 55). Median GLS was -10.0% (-16.3 – -6.4) and median TPSSD was 63 (47 – 87) ms. Three hundred and fifty-eight (40%) patients had an impaired tricuspid annular systolic excursion with a median value of 18 (14 – 22) mm. Detailed information on TTE results can be found in Table 3.

RNV parameter	Study population (*N* = 937)
Gamma camera, *n* (%)	
Symbia T6	647 (69.1)
D-SPECT	290 (30.9)
Radiation dose (MBq)	744 (733 – 757)
Left ventricle	
LVEDVi (ml/m²)	90 (57 – 129)
LVESVi (ml/m²)	55 (22 – 98)
LVEF (%)	38 (23 – 59)
PSD (ms)	43 (19 – 92)
Mean left intraventricular delay (ms)	+2 (-28 – +48)
Right ventricle	
RVEDVi (ml/m²)	96 (74 – 122)
RVESVi (ml/m²)	53 (37 – 74)
RVEF (%)	44.1 ± 13.2
Mean interventricular delay (ms)	+26 (-11 – +79)

Table 2. Radionuclide ventriculography population characteristics (no missing data).
Mean left intraventricular delay was defined as the difference of the time to contraction of the left ventricular lateral wall compared to its septal wall. Mean interventricular delay was defined as the difference of the time to contraction of the RV free wall compared to the left ventricular septal wall. LVEDVi, indexed left ventricle end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end-systolic volume; MBq, mega Becquerel; PSD, phase standard deviation; RNV, radionuclide ventriculography; RVEDVi, indexed right ventricular end-diastolic volume, RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume.

TTE parameter	Study population (*N* = 904)	Missing (of total population)
Delay between TTE and RNV (days)	-1 (-5 – 0)	33 (3.5)
LVEF (%)	36 (25 – 55)	44 (4.7)
LV GLS (%)	-10.0 (-16.3 – -6.4)	226 (24.2)
TPSSD (ms)	63 (47 – 87)	278 (29.7)
TAPSE (mm)	18 (14 – 22)	53 (5.7)
Tricuspid tissular S wave velocity (cm/s)	10 (8 – 13)	77 (8.2)
RV free wall LS	-19.8 ± 7.5	336 (35.9)

Table 3. Transthoracic echocardiography population characteristics.

GLS, global longitudinal strain; LS, longitudinal strain; LV, left ventricular; LVEF, left ventricular ventriculography; RNV, ventriculography; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TPSSD, time-to-peak strain standard deviation; TTE, transthoracic echocardiography.

Outcomes

Events

During a median follow-up of 21 (6 – 38) months, were recorded 320 (34%) events: 85 (9%) ventricular arrhythmias (VA), 69 (7%) heart transplantations (among which 10 (14%) occurred after VA) and 149 (16%) deaths (among which 26 (17%) occurred after VA). The distribution of VAs was the following: 16 (2%) ventricular tachycardias, 6 (1%) ventricular fibrillation, 32 (3%) anti tachycardia pacing, 24 (3%) shocks, 6 (1%) sudden cardiac deaths. Median time to first event was 19 (5 – 35) months.

Univariate analysis

PSD was strongly associated with the occurrence of the composite outcome of VA, heart transplantation or death ($p < 0.0001$). Each 10 ms increase in PSD increased the event hazard by 7% (5 – 9) (Figure 3A).

When assessing each outcome separately using the multistate Cox proportional hazard model, each 10 ms increase in PSD increased the hazard of VA by 12% (9 – 16) ($p < 0.0001$) and the hazard of heart transplantation by 9% (6 – 12) ($p < 0.0001$). A weaker, yet significant, association was observed for the occurrence of death (HR 1.03 (1.00 – 1.05), $p = 0.03$) (Figure 3B, 3C and 3D, Table 4).

	HR (95%CI)	**p-value**
PSD*	1.012 (1.009 – 1.015)	<0.0001
Concordance	0.72 ± 0.03	
Wald test		<0.0001
Robust score test		<0.0001

Table 4. Parameters and performance indices of the multistate survival model focused on VA prediction with PSD.

* Per 1 ms increase. CI, confidence interval; HR, hazard ratio; PSD, left ventricle phase standard deviation; VA, ventricular arrhythmia.

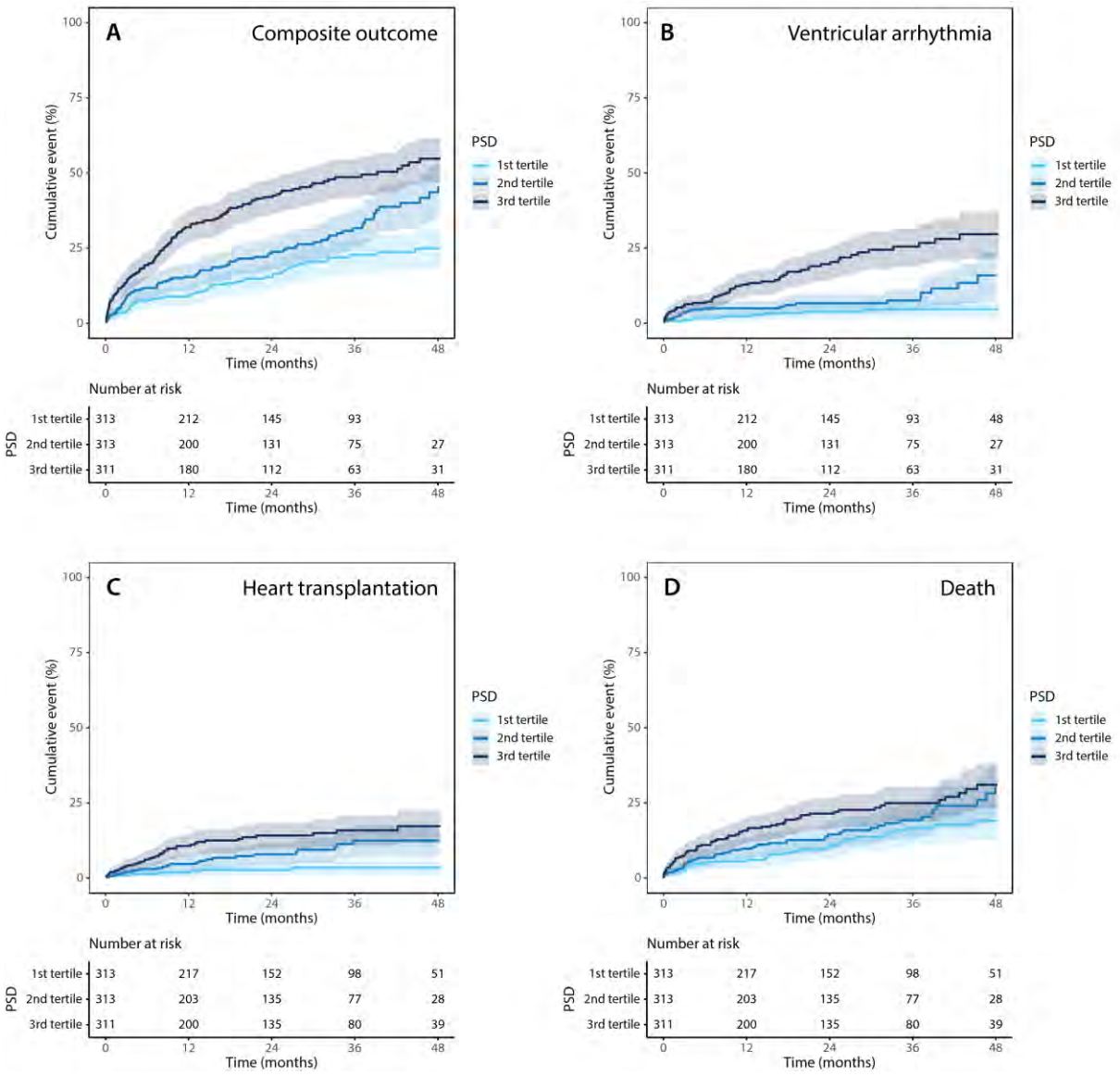


Figure 3. Cumulative event curves.

(A) Composite endpoint (VA, HTx or death) occurrence over time for each PSD tertile. (B) VA occurrence over time for each PSD tertile. (C) HTx occurrence over time for each PSD tertile. (D) Death occurrence over time for each PSD tertile. First tertile: ≤24 ms, Second tertile: 25 to 72 ms, Third tertile: ≥73 ms. HTx, heart transplantation; PSD, left ventricle phase standard deviation; VA, ventricular arrhythmia.

Gamma camera

There was no influence of the gamma camera used for the RNV on the ability of PSD to predict VAs (p for interaction = 0.43).

ICD patients

The results on VAs were confirmed in a subgroup analysis including 331 patients equipped with an ICD in which detection of VA is expected to have perfect sensitivity and specificity (HR 1.07 (1.03 – 1.12), p <0.01).

Underlying cardiomyopathy and previous VAs

The association between PSD and VAs held for ischemic (p <0.0001), dilated non-ischemic (p <0.01) and arrhythmogenic right ventricular cardiomyopathies (p <0.01) but was inverted in patients with channelopathies and idiopathic ventricular arrhythmias (HR 0.08 (0.02 – 0.41), p <0.01). In this latter subgroup, PSD was overall low with little variation (IQR 9 – 22 ms). Other cardiomyopathies had too few events to perform a relevant regression (Supplemental figure 2).

Removing patients with channelopathies or idiopathic ventricular arrhythmias from the model improved its overall performance (concordance 0.75 vs 0.72, robust score test p = 1e-8 vs p = 4e-8).

The association between PSD and VA occurrence was not significantly modified by the existence of previous VAs (HR in primary prevention 1.11 (1.06 – 1.15), HR in secondary prevention 1.08 (1.04 – 1.12), p for interaction = 0.49), nor by previous ventricular tachycardia ablation (HR without ablation 1.12 (1.08 – 1.16), HR with ablation 1.07 (1.00 – 1.15), p for interaction = 0.34).

Established risk factors

Age (HR 1.02 (1.01 – 1.04) per 1-year increase, p <0.01), male sex (HR 2.43 (1.30 – 4.55), p <0.01) and presence of QRS >120 ms (HR 3.22 (2.09 – 4.07), n = 909, p < 0.0001) were significantly associated with the occurrence of VAs in univariate analysis. On TTE examination, LVEF was significantly associated with the occurrence of VAs (HR 0.95 (0.93 – 0.97) per 1% increase, n = 893, p <0.0001), as did LV GLS (HR 1.22 (1.13 – 1.30) per 1% decrease in absolute LV GLS, n = 710, p <0.0001) and TPSSD (HR 1.18 (1.12 – 1.23) per 10 ms increase, n = 659, p <0.0001).

Multivariate analysis

When PSD was assessed alongside with, age, sex, presence of QRS >120 ms, LVEF, LV GLS and TPSSD in multivariate analysis, only PSD and sex remained significantly associated with the occurrence of VAs (respectively p = 0.001, p = 0.03, n = 650) (Table 5).

	HR (95%CI)	**p-value**
Age	1.004 (0.980 – 1.028)	0.76
Male sex	2.982 (1.083 – 8.213)	0.03
QRS >120 ms	1.832 (0.986 – 3.405)	0.06
PSD*	1.008 (1.003 – 1.013)	0.001
LVEF (TTE)	0.989 (0.952 – 1.026)	0.54
LV GLS	1.030 (0.902 – 1.177)	0.66
TPSSD*	1.007 (1.000 – 1.014)	0.06
Concordance	0.80 ± 0.03	
Wald test		<0.0001
Robust score test		<0.0001

Table 5. Parameters and performance indices of the multistate survival model focused on VA prediction with age, sex, QRS >120 ms, PSD, LVEF (as measured by TTE), LV GLS and TPSSD as explanatory variables (n = 650).

* Per 1 ms increase. CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; PSD, left ventricle phase standard deviation; TPSSD, time-to-peak strain standard deviation; TTE, transthoracic echocardiography; VA, ventricular arrhythmia.

Definition of a cutoff for PSD

The best performing cutoff for PSD was 55 ms. In patients without channelopathy or idiopathic ventricular arrhythmias, it exhibited a concordance of 0.69 and an HR of 5.3 (3.1 – 9.1) (n = 898, logrank p <0.0001). The receiver-operator characteristics curve is displayed in Figure 4, with an area under curve of 75% (70 – 80). Sensitivity was 79% and specificity 60%. In this population, negative predictive value was 97% and positive predictive value 16%.

Negative predictive value remained high in patients with depressed LVEF ≤35% (as measured by TTE) with a value of 94%. Even more so in this subpopulation, no VA occurred when PSD was ≤25 ms. These conditions were met in 63 (7%) patients.

As expected, in secondary prevention patients, a cutoff of 55 ms yielded a decreased negative predictive value of 79%.

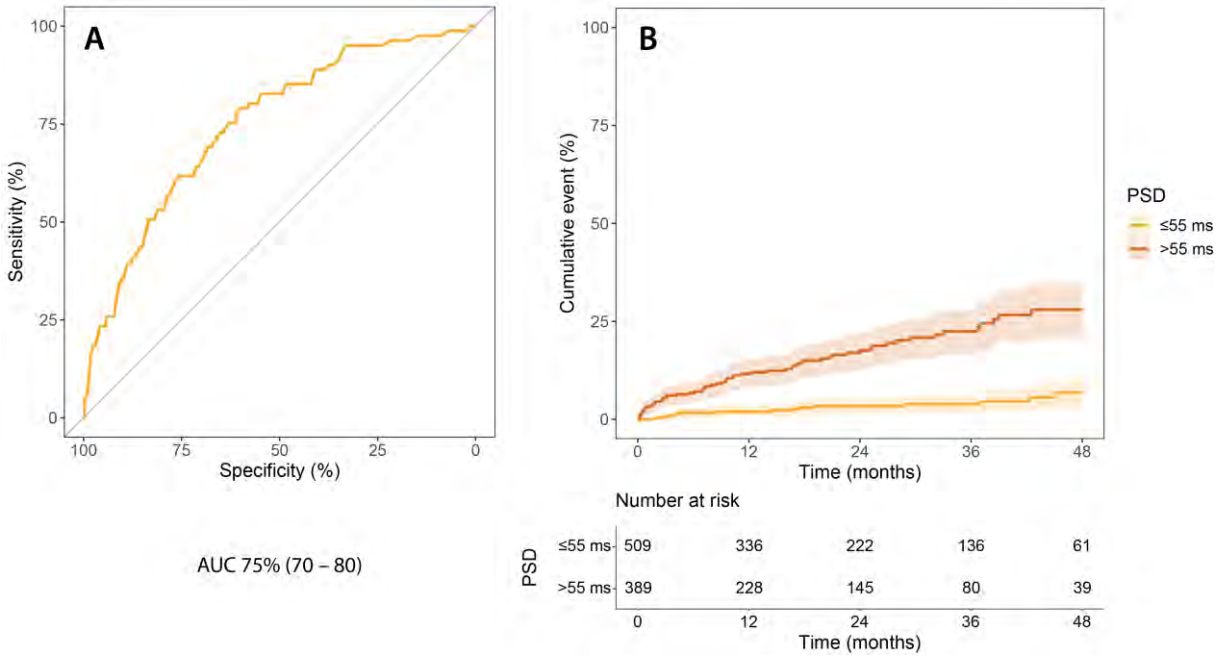


Figure 4. Cutoff performance

Receiver-operator characteristics curve (A) and cumulative event curves (B) for the occurrence of ventricular arrhythmias using a PSD cutoff of ≤55 ms in patients without channelopathy or idiopathic ventricular arrhythmias (n = 898).

AUC, area under curve; PSD, left ventricle phase standard deviation.

Discussion

In this retrospective monocentric observational study, we identified phase standard deviation (LV mechanical dispersion assessed by phase analysis on radionuclide ventriculography) as strongly predictive of malignant ventricular arrhythmia occurrence, even after adjustment for LVEF and LV GLS.

External validity

There is little reference to assess the external validity of our study. Comparison to PSD measured with myocardial perfusion imaging is difficult as this imaging modality implies by itself a bias towards ischemic cardiomyopathy. Furthermore, Pazhenkottil et al.[14] studied major adverse cardiac events rather than VAs specifically, and Uebleis et al.[15] considered LVMD dichotomically and studied death only. Indirectly, external validity seemed fulfilled as we found similar HRs as Haugaa et al.[3] for LVEF and LV GLS ability to predict VAs.

Unlike Zavadovsky et al.,[13] we found an inverse statistical correlation between PSD and VAs in patients with idiopathic ventricular arrhythmias, but our study excluded children.

Interpretation

Mechanical dispersion

Mechanical dispersion is expected to reflect heterogeneity in myocardial contraction that may be secondary to scar, fibrosis, purely mechanical dyssynchrony or any other cause of heterogenous delayed local electrical conduction. Hearts exhibiting these characteristics are prone to ventricular arrhythmias. This need of a structural damage explains why PSD seemed not to be a performing predictor of VA in patients with channelopathies or idiopathic ventricular arrhythmias in our population. We even observed an inverted relationship with higher PSD associated with a reduced event rate. The explanation of this finding remains elusive. Though, considering the narrow range of PSD in this subgroup, it is likely that this association may merely be fortuitous due to sampling. Further evaluation would be needed to confirm this hypothesis.

Each of the up-mentioned abnormalities that contribute to contraction heterogeneity may have their own consequences on depolarization, repolarization and possibly arrhythmogenicity. PSD therefore appears to be a single-measurement encapsulation of this myriad of elements that would be difficult to assess individually. It may serve as a readily accessible, close to pathology, summary of VA risk, even if possibly rough due to the global inclusion of so many potential factors.

We showed that PSD was associated to occurrence of VAs even in patients with previous VAs or previous VT ablation. Patient management (medication, coronary revascularization, reverse remodeling, maybe ablation in itself), may lead to changes in electromechanical heterogeneity and therefore PSD. Hence, PSD would still reflect the evolving arrhythmogenic risk of the underlying cardiomyopathy. However, the existence of patients with normal PSD and a recent history of VA makes negative predictive value weaker in this population.

LVEF and LV GLS both describe an overall performance of myocardial function. Therefore, they bear no information regarding heterogeneity and are outperformed by mechanical dispersion in VA prediction.

PSD and TPSSD are both indices of this mechanical dispersion. Beyond the mere method of measurement, the main difference between these two indices is the myocardial layer involved. PSD being based on blood pool imaging, it necessarily relies the most on the endocardium that is in direct contact with the blood. In contrast, TPSSD, based on General Electric's strain analysis in our study, is derived from full-wall tracking and therefore takes all three myocardial layers into account. Strain analysis performed with a software relying on endocardial layer tracking only might yield TPSSD results closer to PSD. In our model TPSSD was superseded by PSD; we hypothesize that despite the hypothetical increased information given by full-wall tracking, this advantaged is blunted by the inconstant quality of the ultrasonographic window.

Strengths

Population

We describe a mixed and unselected population undergoing RNV. This diverse recruitment is likely to confer a satisfactory degree of generalizability to this study by limiting selection bias and allowing a correct estimation of the effects of PSD. It was nonetheless a rather at-risk population, with a 9% event rate granting sufficient power to the analysis.

Radionuclide ventriculography

The main advantage of RNV is its reliable image quality. There is no window limitation unlike TTE, neither artifacts from implantable electronic devices unlike cardiac magnetic resonance imaging. Despite obvious bias, TPSSD could be obtained from TTE in only 70% of our population.

Fully automated phase analysis grants RNV an excellent reproducibility.[16] General Electric's TTE systems only offer semi-automated strain analysis. The main drawback of full automation is the reduced ability to correct analysis errors or failures. In our experience, it very seldom occurred and essentially concerned cardiac anatomical extremes such as incompletely corrected congenital heart disease or massive aneurysms.

Irregular heart rhythm is often an issue in cardiac imaging. Longitudinal strain measurements fail unless cycles of equivalent lengths are carefully selected. CMR images may be blurred. In contrast, RNV relies on many more beats than TTE and CMR, which allows to trim off cycles that do not fall in an acceptable range around the median cycle length. Hence, RNV may be more accurate in irregular heart rhythms (atrial fibrillation, atrial tachycardia, numerous premature atrial or ventricular complexes), which are common among heart failure patients.

Availability of RNV is a contrasted topic. On one hand, few medical centers have a ward of nuclear medicine. On the other hand, in those which do, RNV is usually far more accessible and with shorter delay than cardiac magnetic resonance imaging.

Events and follow-up

We chose to study "significant" VAs only, excluding non-sustained ventricular tachycardia, in order to limit measurement bias. Otherwise, electronic device-implanted patients or those with repeated 24h ambulatory ECG would have an artificially increased risk of events due to the detection power of these tools. Moreover, "significant" VAs are more likely to be clinically relevant, and accurately detected, as they usually trigger hospitalization or at least medical attention.

Limitations

This study has the same limitations as all monocentric retrospective study. In this specific setting, deaths out of hospital represent a challenge; despite strict definition of sudden death, it is often difficult to gather the precise circumstances of death, even more so years after its occurring. Even when the criteria are met, considering sudden deaths as lethal ventricular arrhythmias can only be a supposition. Nonetheless, sudden deaths were rare in our study which limits their impact on our results.

Median follow-up was almost two years. Whenever possible we reached out to the subject's general practitioner or cardiologist to improve available follow-up data. Yet, follow-up

period still falls below the reported ones of studies dedicated to TPSSD. This is partly explained by the rather high death rate of this severely ill population.

No adjustment could be performed with other usual markers of VA risk (heart rate variability, T wave alternans, signal-averaged electrocardiogram, late gadolinium enhancement, etc.). thus, it is not possible to exclude that PSD may not be an independent predictor of VA. Such analysis could only be made in large prospective trials.

We did not allow for the possibility that PSD may be subject to change over time (progression of fibrosis, new myocardial infarction, etc.). It might therefore not be the best suited parameter to predict events occurring remotely from the RNV.

The major inconvenient in RNV is the radiation exposure that is absent in TTE and CMR. Although, it is rather limited, and patients the most susceptible to radiation —pregnant women— are excessively rare in the target population.

In our study, the same post-processing software for all patients but RNV images were acquired with two different gamma cameras. D-SPECT gamma cameras yielded higher PSD values, though it did not alter the ability of PSD to predict VAs. In the absence of direct comparison of RNV results in the same patient with both cameras, it is reasonable to assume that the D-SPECT camera was used in more ill patients.

Perspectives

After confirmation with adequately designed randomized trials, PSD could be used to guide ICD implantation, whether as a replacement of LVEF or in conjunction. In the latter case, due to its excellent negative predictive value, PSD could avoid unnecessary ICDs (and related complications) to patients at low risk of VA despite severely depressed LVEF.

Conclusion

In this single-centered retrospective cohort study, the occurrence of ventricular arrhythmias could be predicted by left ventricular mechanical dispersion assessed by phase analysis on radionuclide ventriculography, independently of established risk factors, including left ventricular ejection fraction and global longitudinal strain.

Vu permis d'imprimer
Le Doyen de la Faculté
De Médecine Rangueil

E. SERRANO
21.06.2021

Vu et Accordé du Jury

Professeur Michel GALINIER
Chef de Service
Fédération des services de Cardiologie
CHU de Toulouse – Hôpital Rangueil
Tél. 05 61 32 26 61

References

1. Marwick TH. Ejection Fraction Pros and Cons. J Am Coll Cardiol 2018;72(19):2360–79.

2. Kawakami H, Nerlekar N, Haugaa KH, Edvardsen T, Marwick TH. Prediction of Ventricular Arrhythmias With Left Ventricular Mechanical Dispersion. JACC Cardiovasc Imaging [Internet] 2019 [cited 2019 Dec 10];Available from: https://linkinghub.elsevier.com/retrieve/pii/S1936878X19304309

3. Haugaa KH, Grenne BL, Eek CH, et al. Strain Echocardiography Improves Risk Prediction of Ventricular Arrhythmias After Myocardial Infarction. JACC Cardiovasc Imaging 2013;6(8):841–50.

4. Haugaa KH, Smedsrud MK, Steen T, et al. Mechanical Dispersion Assessed by Myocardial Strain in Patients After Myocardial Infarction for Risk Prediction of Ventricular Arrhythmia. JACC Cardiovasc Imaging 2010;3(3):247–56.

5. Ersbøll M, Valeur N, Andersen MJ, et al. Early Echocardiographic Deformation Analysis for the Prediction of Sudden Cardiac Death and Life-Threatening Arrhythmias After Myocardial Infarction. JACC Cardiovasc Imaging 2013;6(8):851–60.

6. Haugaa KH, Goebel B, Dahlslett T, et al. Risk Assessment of Ventricular Arrhythmias in Patients with Nonischemic Dilated Cardiomyopathy by Strain Echocardiography. J Am Soc Echocardiogr 2012;25(6):667–73.

7. Candan O, Gecmen C, Bayam E, Guner A, Celik M, Doğan C. Mechanical dispersion and global longitudinal strain by speckle tracking echocardiography: Predictors of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy. Echocardiography 2017;34(6):835–42.

8. Trivedi SJ, Campbell T, Stefani LD, Thomas L, Kumar S. Strain by speckle tracking echocardiography correlates with electroanatomic scar location and burden in ischaemic cardiomyopathy. Eur Heart J - Cardiovasc Imaging 2021;jeab021.

9. Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: effect of biventricular pacing to correct interventricular dyssynchrony. J Am Coll Cardiol 2000;35(5):1221–7.

10. Tournoux F, Chequer R, Sroussi M, et al. Value of mechanical dyssynchrony as assessed by radionuclide ventriculography to predict the cardiac resynchronization therapy response. Eur Heart J – Cardiovasc Imaging 2016;17(11):1250–8.

11. Aernout Somsen G, Verberne HJ, Burri H, Ratib O, Righetti A. Ventricular mechanical dyssynchrony and resynchronization therapy in heart failure: a new indication for Fourier analysis of gated blood-pool radionuclide ventriculography: Nucl Med Commun 2006;27(2):105–12.

12. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Ventricular Dyssynchrony and Risk Markers of Ventricular Arrhythmias in Nonischemic Dilated Cardiomyopathy:. A Study with Phase Analysis of Angioscintigraphy. Pacing Clin Electrophysiol 2003;26(1p2):352–6.

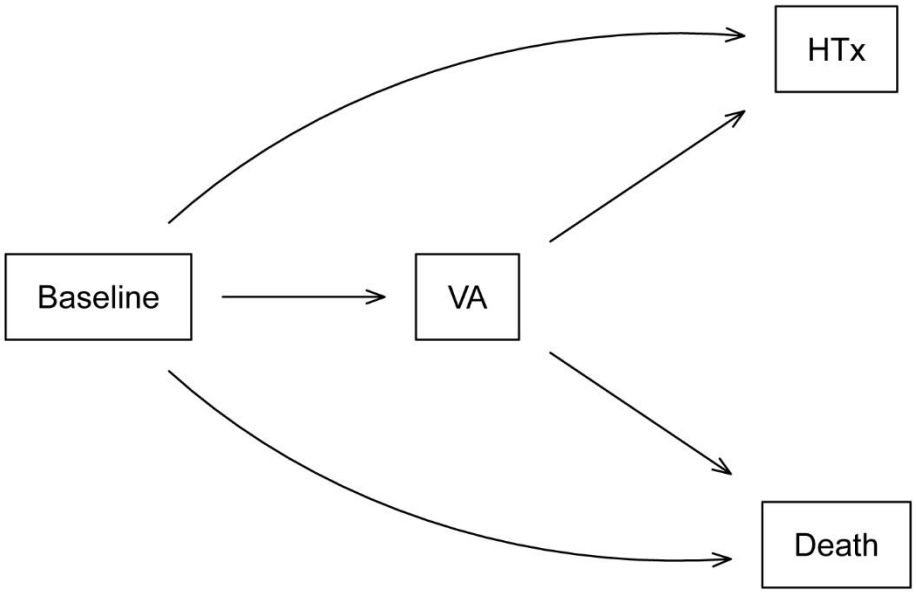
13. Zavadovsky KV, Saushkin VV, Khlynin MS, Popov SV, Lishmanov YB. Radionuclide Assessment of Cardiac Function and Dyssynchrony in Children with Idiopathic Ventricular Tachycardia: RADIONUCLIDE DIAGNOSIS OF VENTRICULAR ARRHYTHMIAS. Pacing Clin Electrophysiol 2016;39(11):1213–24.

14. Pazhenkottil AP, Buechel RR, Husmann L, et al. Long-term prognostic value of left ventricular dyssynchrony assessment by phase analysis from myocardial perfusion imaging. Heart 2011;97(1):33–7.

15. Uebleis C, Hellweger S, Laubender RP, et al. Left ventricular dyssynchrony assessed by gated SPECT phase analysis is an independent predictor of death in patients with advanced coronary artery disease and reduced left ventricular function not undergoing cardiac resynchronization therapy. Eur J Nucl Med Mol Imaging 2012;39(10):1561–9.

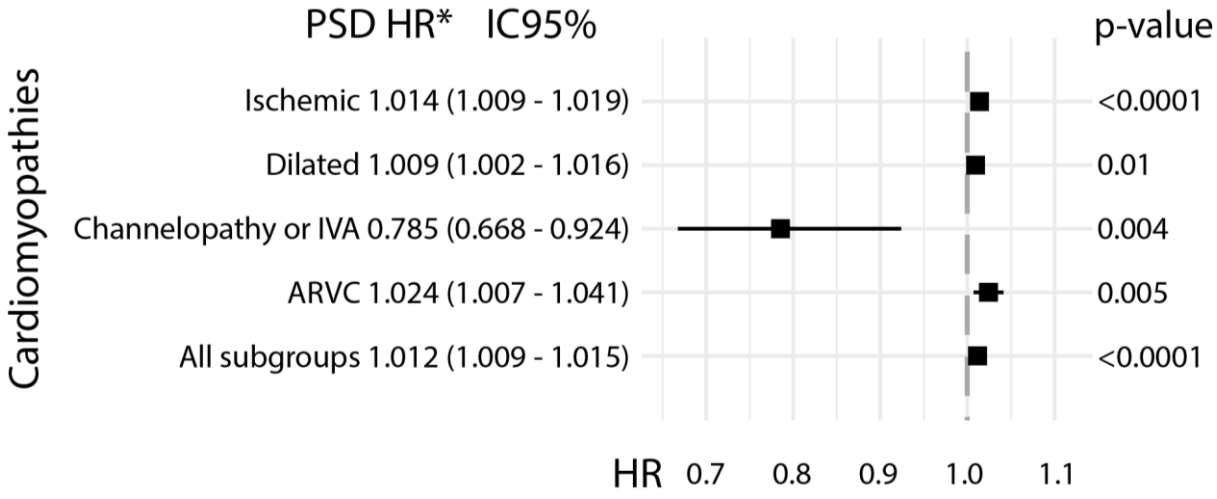
16. Singh H, Singhal A, Sharma P, Patel CD, Seth S, Malhotra A. Quantitative assessment of cardiac mechanical synchrony using equilibrium radionuclide angiography. J Nucl Cardiol 2013;20(3):415–25.

Supplemental figures



Supplemental figure 1. State figure of the multistate survival model.

HTx, heart transplantation; VA, ventricular arrhythmia.



Supplemental figure 2. Univariate analysis of the association of PSD with the occurrence of VAs according to cardiomyopathy subgroup.

* Per 1 ms increase. CI, confidence interval; HR, hazard ratio; IVA, idiopathic ventricular arrhythmia; PSD, left ventricular phase standard deviation.

Supplemental material

Cutoff selection

Best performing cutoff for PSD was selected according to survival analysis. In order to optimize both significance and performance of the logrank test, we used a composite index I defined as

$$I = -log_{10}(p_{rob}) \times C$$

where p_{rob} is the p-value of the robust score test and C is the centered and scaled concordance of the model.

Weighting

Analyses involving TTE measurements were weighted according to W, defined as

$$W = \frac{7}{7 - |\Delta t|}$$

Where Δt is the time gap expressed in days between the TTE and the RNV for each patient.

Statistical analysis references

R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Stefan Milton Bache and Hadley Wickham (2020). magrittr: A Forward-Pipe Operator for R. R package version 2.0.1. https://CRAN.R-project.org/package=magrittr

Wickham et al., (2019). Welcome to the tidyverse. Journal of Open Source Software, 4(43), 1686, https://doi.org/10.21105/joss.01686

Hadley Wickham, Romain François, Lionel Henry and Kirill Müller (2021). dplyr: A Grammar of Data Manipulation. R package version 1.0.6. https://CRAN.R-project.org/package=dplyr

H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016.

Garrett Grolemund, Hadley Wickham (2011). Dates and Times Made Easy with lubridate. Journal of Statistical Software, 40(3), 1-25. URL https://www.jstatsoft.org/v40/i03/.

Therneau T (2021). *A Package for Survival Analysis in R*. R package version 3.2-11, https://CRAN.R-project.org/package=survival

Terry M. Therneau, Patricia M. Grambsch (2000). *Modeling Survival Data: Extending the Cox Model*. Springer, New York. ISBN 0-387-98784-3.

Liesbeth C. de Wreede, Marta Fiocco, Hein Putter (2011). mstate: An R Package for the Analysis of Competing Risks and Multi-State Models. Journal of Statistical Software, 38(7), 1-30. https://www.jstatsoft.org/v38/i07/.

Liesbeth C. de Wreede, Marta Fiocco, Hein Putter (2010) The {mstate} Package for Estimation and Prediction in Non- and Semi-Parametric Multi-State and Competing Risks Models. Computer Methods and Programs in Biomedicine, 99, 261-274.

Hein Putter, Marta Fiocco, and Ronald B. Geskus (2007) Tutorial in Biostatistics: Competing Risks and Multi-State Models. Statistics in Medicine, 26, 2389-2340.

Xavier Robin, Natacha Turck, Alexandre Hainard, Natalia Tiberti, Frédérique Lisacek, Jean-Charles Sanchez and Markus Müller (2011). pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics, 12, p. 77. DOI: 10.1186/1471-2105-12-77 http://www.biomedcentral.com/1471-2105/12/77/

Weiliang Qiu, Jorge Chavarro, Ross Lazarus, Bernard Rosner and Jing Ma. (2021). powerSurvEpi: Power and Sample Size Calculation for Survival Analysis of Epidemiological Studies. R package version 0.1.3. https://CRAN.R-project.org/package=powerSurvEpi

PRÉDICTION DES ARYTHMIES VENTRICULAIRES PAR L'ANALYSE DE PHASE EN VENTRICULOGRAPHIE ISOTOPIQUE

Résumé : La prédiction des arythmies ventriculaires repose actuellement essentiellement sur la fraction d'éjection du ventricule gauche, connue pour présenter de nombreuses limitations. La dispersion électromécanique a récemment émergé comme un paramètre échocardiographique plus performant. L'analyse de phase du ventricule gauche par ventriculographie isotopique permet également d'évaluer la dispersion électromécanique mais sa valeur prédictive n'était jusque-là pas connue. Dans ce travail, il est démontré que l'analyse de phase permet également une bonne prédiction des arythmies ventriculaires malignes chez une population de patients non sélectionnés.

PHASE ANALYSIS FOR VENTRICULAR ARRHYTHMIA PREDICTION

Abstract: The identification of patients at-risk of ventricular arrhythmias (VAs) and sudden cardiac death remains a challenge that is incompletely addressed by left ventricular ejection fraction (LVEF) alone. Mechanical dispersion has recently emerged as parameter with better performance than LVEF that could be measured with speckle-tracking echocardiography. Mechanical dispersion can also be measured with phase standard deviation (PSD) on tomographic radionuclide ventriculography. Although, whether if PSD is able to predict VAs is unknown. In this study, we demonstrate that the occurrence of ventricular arrhythmias could be predicted by left ventricular mechanical dispersion assessed by phase analysis on radionuclide ventriculography, even after adjustment for LVEF and left ventricular global longitudinal strain.

Mots-clés : Dispersion électromécanique, arythmies ventriculaires, mort subite, ventriculographie isotopique

Keywords: Mechanical dispersion, phase, ventricular arrhythmia, sudden cardiac death, radionuclide ventriculography, gated tomographic equilibrium blood-pool imaging

Discipline administrative : Médecine spécialisée clinique

Université Toulouse III-Paul Sabatier
Faculté de médecine Toulouse-Purpan,
37 Allées Jules Guesde 31000 Toulouse

Directeur de thèse : Pr Philippe MAURY