ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικό και Καποδιστριακό
Πανεπιστήμιο Αθηνών

ΠΜΣ: Παγκόσμια Υγεία-Ιατρική των καταστροφών

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Διπλωματική εργασία

Endomyocardial fibrosis and Chagas Disease: the neglected cardiomyopathies and the promising role of cardiac magnetic resonance in diagnosis. A Systematic Review

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Abstract:
Endomyocardial fibrosis(EMF) and Chagas Disease(ChD) constitute the so-called neglected cardiomyopathies.EMF ,a disease of unknown etiology, endemic in Equatorial Africa is the most common restrictive cardiomyopathy in the world. Mysteriously large fibrotic plagues occupy the cardiac apex and the subvalvular apparatus. Chagas disease, highly endemic in Latin America, is a zooanthroponosis caused by the protozoa Trypanosoma Cruzi. Notwithstanding that the epidemiology of the two diseases is very distinct it seems they also share similarities. Endemicity to the tropics, strong correlation with poverty and parasitic infections, poorly understood and insidious natural course, lack of effective treatment, poor prognosis, appearance in non-endemic settings and high misdiagnosis rates characterize these conditions and justify their characterization as "neglected". Cardiac magnetic resonance (CMR), a novel imaging modality with capability of tissue characterization could illuminate the course of the diseases and play a crucial role in early diagnosis and risk stratification. In an attempt to raise awareness of the forgotten cardiomyopathies, we conducted a systematic review of the literature including the application of CMR as a novel diagnostic weapon.

Key words: endomyocardial fibrosis, endomyocardial sclerosis, chagas disease, chagasic cardiomyopathy, restrictive cardiomyopathy, CMR, MRI ,late gadolinium enhancement

Περίληψη:

Το κλινικό σύνδρομο της καρδιακής ανεπάρκειας έχει πάρει διαστάσεις πανδημίας ωστόσο οι αιτίες του διαφέρουν μεταξύ του αναπτυσόμενου και του ανεπτυγμένου κόσμου. Στον αναπτυσσόμενο κόσμο η Ενδομυοκαρδιακή Ίνωση και η νόσος του Chagas αποτελούν τις κύριες αιτίες καρδιακής ανεπάρκειας σε άτομα χαμηλών κοινωνικοικονομικών στρωμάτων.Η Ενδομυοκαρδιακή Ίνωση και η Νοσος Chagas παρότι πλήττουν 8 και 12 εκατομμύρια ασθενείς αντιστοιχως χαρακτηρίζονται ως «ξεχασμένες μυοκαρδιοπάθειες».Η επιδημιολογία και η ακριβής παθοφυσιολογία των εν λόγω νοσημάτων παραμένει μυστήριο ενώ αποτελεσματικές θεραπείες δεν υπάρχουν.

Τις τελευταίες δεκαετίες μια νέα απεικονιστική μέθοδος,η μαγνητική τομογραφία καρδιάς έχει προστεθεί στην διαγνωστική μας φαρέτρα. Σκοπός της παρούσας συστηματικής ανασκόπησης είναι να παραθέσει μια σύνοψη της υπάρχουσας βιβλιογραφίας πάνω στις ξεχασμένες μυοκαρδιοπάθειες αναδεικνύοντας παράλληλα τις εφαρμογές της μαγνητικής τομογραφίας καρδιας στην διάγνωση τους.

Μέθοδοι:

Κατά τη διενέργεια της συστηματικής ανασκόπησης αναζητήθηκαν άρθρα στις βάσεις δεδομένων Pubmed/Medline και Scielo. Οι λέξεις κλειδιά που χρησιμοποιήθηκαν ήταν: Ενδομυοκαρδιακή Ίνωση ή «Νόσος Chagas» ή «Περιοριστική Μυοκαρδιοπάθεια » ΚΑΙ «επιδημιολογία» ή «αιτιολογία» ή «διάγνωση» ή «CMR» ή «MRI» ή καθυστερημένος εμπλουτισμός ή χαρακτηρισμός ιστού ή «χαρτογράφηση T1» ή «κλάσμα εξωκυττάριου όγκου». Οι προαναφερθέντες όροι αναζητήθηκαν στα αγγλικά και στα ισπανικά. Εν τέλει ,138 άρθρα επιλέγησαν για να συμπεριληφθουν στην εργασία.

Ενδομυοκαρδιακή ίνωση:

Η ενδομυοκαρδιακή ίνωση αποτελεί το συχνότερο αίτιο περιοριστικής μυοκαρδιοπάθειας παγκοσμίως. Ενδημεί κυρίως στην Υποσαχάρια Αφρική και τη νοτιοανατολική Ασία ενώ περιστατικά έχουν αναφερθεί και στην επαρχία Guanxi της Κίνας. Η νόσος προσβάλει συχνότερα άτομα 10-30 ετών. Η παθογένεση και η ακριβής αιτιολογία της ενδομυοκαρδιακής ίνωσης δεν έχουν διαλευκανθεί. Παράγοντες που έχουν ενοχοποιηθεί είναι η φτώχεια, η διατροφή πτωχή σε μαγνήσιο, η υπερηωσινοφιλία, οι παρασιτικές λοιμωξεις και η γενετική προδιάθεση.

Η νόσος φαίνεται να διαδράμει σε 3 στάδια: i)οξέια φάση ii) τη λανθάνουσα ενδιάμεση φάση iii) τη χρόνια ινωτική φάση. Η οξεία φάση της νόσου εμφανίζεται κλινικά με πυρετό ,περιοφθαλμικό οίδημα, κνησμό, εξάνθημα και μυοκαρδίτιδα.Στην φάση αυτή η διήθηση του μυοκαρδίου από ηωσινόφιλα οδηγει σε πάχυνση τοιχωμάτων και σχηματισμό ενδοτοιχωματικών θρόμβων. Τα συμπτώματα συνήθως υποστρέφουν και η νόσος μεταπίπτει στη λανθανουσα ενδιάμεση φάση.Παρόλα αυτά, η ανάπτυξη κεραυνοβόλου μυοκαρδίτιδας με πολύ βαριά πρόγνωση και θάνατο αναφέρεται σπανιότερα στη βιβλιογραφία.Η ενδιάμεση φάση της νόσου χαρακτηρίζεται από εξάρσεις και υφέσεις ενώ απουσιάζει η διήθηση από φλεγμονώδη κύτταρα και αναπτύσεται σταδιακά ινωση στο προσβεβλημμένο μυοκάρδιο.Οι παράγοντες που συνεπικουρούν στην ταχύτητα μετάπτωσης της νόσου στην χρόνια φάση παραμένουν άγνωστοι.Η χρόνια ινωτική φάση εκδηλώνεται με καχεξία υποαλβουμιναιμία οίδημα παρωτίδων ,υπέρχρωση χειλέων ,κεντρική κυάνωση, ασκιτική συλλογή απουσία οιδήματος σφυρών και ηπατοσπληνομεγαλία.Στην καρδιά,ευμεγέθεις ινωτικές πλάκες αναπτύσσονται στο υπενδοκάρδιο επεκτεινόμενες σταδιακά από την κορυφή προς την υποβαλβιδική συσκευή.Η κορυφή της καρδιάς συχνά καταλαμβάνεται από θρόμβο. Η ίνωση της υποβαλβιδικής συσκευής προκαλεί παγίδευση τενόντιων χορδών και θηλοειδών μυών περιορισμό στην κίνηση των γλωχίνων των κολποκοιλιακών βαλβίδων και τελικά σοβαρή ανεπάρκεια μιτροειδούς και τριγλώχινας. Χαρακτηριστικά απουσιάζει η προσβολή του

χώρου εξόδου τόσο της αριστερής όσο και της δεξιάς κοιλίας.Οι ασθενείς καταλήγουν συνηθέστερα από μαζική πνευμονική εμβολή ,συστηματική εμβολή ή ηπατική ανεπάρκεια.

Η διάγνωση της ενδομυοκαρδιακής ίνωσης γίνεται συνήθως με υπερηχοκαρδιογραφημα.Συχνά ευρήματα της υπερηχοκαρδιογραφικής μελέτης είναι η αμφικολπική διάταση σοβαρή ανεπάρκεια μιτροειδούς ή/και τριγλώχινας και κατάληψη της κορυφής από ινώδη ιστό και ενίοτε θρόμβο.Κατά τη μελέτη με παλμικό Doppler, χαρακτηριστικό είναι το περιοριστικό πρότυπο πλήρωσης(E>>A) και η σοβαρή διαστολική δυσλειτουργία (E/e'>14). Το ΗΚΓ παρουσιάζει μη ειδικά ευρήματα όπως διαταραχές του ST και χαμηλά δυναμικά.Στην απλή ακτινογραφία θώρακος ανευρίσκεται αυξημένος καρδιοθωρακικός δείκτης και ενίοτε περικαρδιακή συλλογή. Η διαφορική διάγνωση της ενδομυοκαρδιακής ίνωσης περιλαμβάνει μεταξύ άλλων την ανωμαλία Ebstein, την υπερτροφική μυοκαρδιοπάθεια κορυφής, τη ρευματική καρδιακή νόσο, τη συμπιεστική περικαρδίτιδα, την αμυλοείδωση και την καρδιακή σαρκοείδωση.

Η θεραπεία της νόσου περιλαμβάνει τη λήψη κορτικοειδών χωρίς όμως το ώφελος να έχει επιβεβαιωθέι από κλινικές δοκιμες. Η κλασική φαρμακευτική θεραπεία της καρδιακής ανεπάρκειας χορηγείται και σε ασθενείς με ενδομυοκαρδιακή ίνωση για την βελτίωση των συμπτωμάτων.Η μοναδική θεραπευτική παρέμβαση η οποία φαίνεται να επηρεάζει την πρόγνωση των ασθενών με ενδομυοκαρδιακή ίνωση είναι η χειρουργική επέμβαση.Ασθενείς με ενδομυοκαρδιακή ίνωση και καρδιακή ανεπάρκεια κλάσης III/IV κατά NYHA έχουν ένδειξη για χειρουργείο εφόσον δεν φέρουν μη αναστρέψιμες ηπατικές ή καρδιακές βλάβες. Η ενδομυοκαρδεκτομή με αντικατάσταση ή επιδιόρθωση των προσβεβλημένων κολποκοιλιακών βαλβίδων όπου κρίνεται απαρραιτητο αποτελεί την ενδεδειγμένη χειρουργική θεραπεία. Η περιεγχειρητική θνητότητα υπολογίζεται στο 20% ενώ η περιορισμένη προσβασιμότητα των ασθενών σε καρδιοχειρουργικά κέντρα αποτελεί τροχοπέδη στην αποτελεσματική αντιμετώπιση της νόσου.

Νόσος Chagas:

Η νόσος Chagas είναι μια ανθρωποζωονόσος ενδημική στη λεκάνη του ποταμού Αμαζόνιου που μεταδίδεται στον άνθρωπο μέ το πρωτόζωο Trypanosoma Cruzi. Οι κύριοι τρόποι μετάδοσης του τρυπανοσώματος είναι: i) διαμέσου δήγματος ενός ενδιάμεσου εντόμου ξενιστή , ιι) κατανάλωση μολυσμένων τροφίμων και ποτών, iii) μολυσμένη μετάγγιση αίματος, iv)μεταμόσχευση όργάνου από μολυσμένο δότη, v) κάθετα από τη μολυσμένη μητέρα στο κύημα.Στη Λατινική Αμερική,σημαντικές προσπάθειες έχουν καταβληθεί τις τελευταίες δεκαετίες τόσο για την εξάλειψη του εντόμου που μεταφέρει το τρυπανόσωμα στον άνθρωπο όσο και για τον ενδελεχή έλεγχο των μεταγγιζόμενων προιόντων αίματος. Η μετανάστευση μολυσμένων ατόμων

από τη Λατινική Αμερική στον υπόλοιπο κόσμο άλλαξε ριζικά την επιδημιολογία της νόσου Chagas και προκάλεσε την εμφάνιση της σε μη ενδημικές χώρες..

Μετά τον ενοφθαλμισμό του Τρυπανοσώματος στο ανθρώπινο σώμα, μεσολαβει περίοδος επώασης 2 εβδομάδων μέχρι την έναρξη της οξείας φάσης της νόσου η οποία διαρκεί περίπου 2 μήνες.Μετά την ολοκλήρωση της οξείας φάσης το 75% των μολυσμένων ατόμων εισέρχονται στη λανθάνουσα φάση της νόσου η οποία διαδράμει με εξάρσεις και υφέσεις.Μια εως δύο δεκαετίες αργότερα,το 1/3 των αρχικών μολυσμένων ατόμων θα αναπτύξουν τη μυοκαρδιοπάθεια της νόσου Chagas η οποία έχει βαρύτατη πρόγνωση.

Κλινικά η νόσος κατά την οξεία φάση εκδηλώνεται με πυρέτιο,μυαλγίες ,εφίδρωση, διάρροια,έμετο λεμφαδενοπάθεια και ηλεκτροκαρδιογραφικές αλλοιώσεις (χαμηλα δυναμικά ,διαταραχές ST κ.α). Σε ορισμένες περιπτώσεις χαρακτηριστικά είναι τα Τσαγκώματα(Chagomas) -φλεγμονώδη οζίδια στον τόπο ενοφθαλμισμού του πρωτοζώου.Ασθενείς που προσεβλήθησαν από το Τρυπανόσωμα διαμέσου κατανάλωσης μολυσμένης τροφής εμφανίζουν βαρύτερη νόσο με ηπατοσπληνομεγαλία και αιμορραγικό ίκτερο.Αξίζει να σημειωθεί ότι στο 1% των ασθενών με οξέια νόσο, ανεξαρτήτως τρόπου μετάδοσης, αναπτύσσεται κεραυνοβόλος μυοκαρδίτιδα και/ή εγκαφαλομυελίτιδα που επιφέρουν το θάνατο.Οι ασθενείς που μεταπίπτουν στην ενδιάμεση φάση της νόσου είναι άτομα ασυμπτωματικα, με φυσιολογικό ΗΚΓ,φυσιολογική ακτινογραφία θώρακος τα οποία ωστόσο έχουν θετικές ορολογικές δοκιμασίες για Trypanosoma Cruzi.Η μετάπτωση από την ενδιάμεση στη χρόνια μορφή της νόσου γίνεται με ρυθμό 5% ετησίως.

Όταν εγκατασταθεί, η μυοκαρδιοπάθεια την νόσου Chagas, αυτή εκδηλώνεται με τρία κλινικά σύνδρομα: i) αρρυθμιογόνο σύνδρομο, ii) καρδιοεμβολισμός και εγκεφαλικά επεισόδια, iii)καρδιακή ανεπάρκεια. Συχνή είναι η εμφάνιση τόσο βραδυαρρυθμιών όσο και ταχυαρρυθμιών. Νόσος φλεβοκόμβου,2^{ου} ή 3^{ου} βαθμού κολποκοιλιακός αποκλεισμός, αποκλεισμοί αριστερού ή δεξιού σκέλους ,πρώιμες κοιλιακές συστολές και κακοήθεις κοιλιακές αρρυθμίες μπορεί να εμφανιστούν μεταξύ άλλων.Τα καρδιοεμβολικά φαινόμενα συχνά παρουσιάζονται σε νεαρούς ασθενείς με νόσο Chagas και μπορεί να είναι η πρώτη εκδήλωση της νόσου.Παράγοντες που συνεπικουρούν στην εκδήλωση τους είναι οι ενδοκαρδιακοί θρόμβοι,η διάταση αριστερού κόλπου τα ανευρύσματα κορυφής(επίσης συχνά απαντόμενα στη νόσο Chagas) και η κολπική μαρμαρυγή. Η χρόνια μορφή της νόσου Chagas οδηγεί σε διατατικού τύπου μυοκαρδιοπάθεια και τελικά σε δεξιά ή /και αριστερή καρδιακή ανεπάρκεια.

Η διάγνωση της νόσου κατά την οξεία φάση πραγματοποιείται με άμεση παρατήρηση του Τρυπανοσώματος κατά τη μικροσκόπηση αίματος του ασθενούς. Στην ενδιάμεση και την χρόνια

φάση η παρασιταιμία απουσιάζει χαρακτηριστικά και η διάγνωση επιβεβαιώνεται με ορολογικές δοκιμασίες που ανιχνεύουν anti-T.Cruzi IgG. Στο ΗΚΓ δεν υπάρουν ευρήματα παθογνωμονικά για τη νόσο, ωστόσο η ανευρεση αποκλεισμού δεξιού σκέλους με προσθιο αριστερο ημισκελικό αποκλεισμό εγείρει έντονα την υποψία για Chagas σε ασθενή με συμβατό επιδημιολογικό υπόβαθρο.Το υπερηχογράφημα αναδεικνύει περικαρδιακή συλλογή και μειωμένο κλάσμα εξώθησης. Κοιλιακά ανευρύσματα κορυφής και τμηματικές διαταραχές κινητικότητας στο κατώτερο πλάγιο τοίχωμα και την κορυφή είναι επίσης χαρακτηριστικά της νόσου.Στη Doppler μελέτη ανιχνευεται συχνά λειτουργική ανεπάρκεια των κολποκοιλιακών βαλβίδων λόγω διάτασης του δακτυλίου.

Η θεραπεία της καρδιακής ανεπάρκειας στη νόσο Chagas αποτελεί πρόκληση. Κατευθυντήριες οδηγίες για τη μυοκαρδιοπάθεια της νόσου Chagas δεν υπάρχουν και συνεπώς ακολουθείται η τυποποιημένη φαρμακευτική θεραπεία καρδιακής ανεπάρκειας μη ισχαιμικού τύπου. Συγκεκριμένα ενδείκνειται η χρήση ανταγωνιστων μετατρεπτικού ενζύμου αγγειοτενσίνης,ανταγωνιστων υποδοχέων αγγειοτενσίνης 1, β- αποκλειστών, διουρητικών και ινότροπων φάρμακων.Σε ασθενείς με συνυπάρχουσα κολπική μαρμαρυγή ,κοιλιακό ανευρυσμα ή καρδιακό θρόμβο απαιτείται και η προσθήκη αντιπηκτικής αγωγής.Στη θεραπεία των αρρυθμιών της νόσου Chagas, η αμιωδαρόνη χρησιμοποιείται ως φάρμακο πρώτης γραμμής ενώ θέση έχει και η εμφύτευση απινιδωτή σε ασθενείς που εμφανίζουν κοιλιακή ταχυκαρδία. Σε υψηλού βαθμού κολποκοιλιακούς αποκλεισμούς ή νόσο φλεβοκόμβου οι ασθενείς με νόσο Chagas ωφελούνται απο την εμφύτευση βηματοδότη.Αντιπαρασιτικά φάρμακα για την εκρίζωση του Τρυπανοσώματος έχουν επίσης θέση στη θεραπευτική φαρέτρα. Η βεζνιδαζόλη και το nifurtimox χρησιμοποιούνται με ικανοποιητικά αποτελέσματα ιδιαίτερα στην οξεία φάση της νόσου, ωστόσο έχουν σημαντικές ανεπιθύμητες ενέργειες και δεν επηρεάζουν την έκβαση των ασθενών εφόσον εγκατασταθεί η μυοκαρδιοπάθεια.

Εφαρμογές της μαγνητικής τομογραφίας καρδιάς στις ξεχασμένες μυοκαρδιοπάθειες:

Η μαγνητική τομογραφία καρδιάς έχει φέρει τις τελευταίες δεκαετίες επανάσταση στην ακριβή διάγνωση των μυοκαρδιοπαθειών. Με τη συγκεκριμένη εξέταση μπορούν να αξιολογηθούν ταυτόχρονα η ανατομία, η λειτουργικότητα, η αιμάτωση και η βιωσιμότητα της καρδιάς. Το μεγαλύτερο πλεονέκτημα της μαγνητικής όμως αποτελεί αδιαμφισβήτητα η δυνατότητα ακριβούς χαρακτηρισμού ιστών και η ποσοτικοποίηση της ίνωσης και του οιδήματος του μυοκαρδίου με τη βοήθεια των τεχνικών του καθυστερημένου εμπλουτισμού και της T1/T2 χαρτογράφησης.

Δεδομένου ότι δεν υπάρχει συγκεκριμένο πρωτόκολλο για τις ξεχασμένες μυοκαρδιοπάθειες, εφαρμόζεται το πρωτόκολλο απεικόνισης των μη ισχαιμικού τύπου μυοκαρδιοπαθειών σύμφωνα με τις οδηγίες της Society of Cardiovascular Magnetic Resonance (SCMR).

Στην ενδομυοκαρδιακή ίνωση παρατηρούμε καθυστερημένο εμπλουτισμό του γαδολινίου στο υπενδοκάρδιο της κορυφής και του χώρου εισόδου χωρίς κατανομή άρδευσηςστεφανιαίου αγγείου. Ένα άλλο εύρημα που έχει περιγραφεί είναι η εμφάνιση τριών στρωμάτων της καρδιακής κορυφής με χαμηλού σήματος φυσιολογικό μυοκάρδιο και παχυσμένο ινωτικό ενδομυοκάρδιο το οποίο καταλαμβάνεται από χαμηλού σήματος επασβεστωμένο θρόμβο κορυφής. Το άνωθεν εύρημα ονομάζεται σημείο double V και θεωρείται χαρακτηριστικό της νόσου.Η μαγνητική τομογραφία καρδιάς φαίνεται να έχει πληθώρα εφαρμογών στην διάγνωση και θεραπεία της ενδομυοκαρδιακής ίνωσης. Συγκεκριμένα, σε ασθενείς με τυπικα ευρήματα καθυστερημένου εμπλουτισμού γαδολινίου η μαγνητική τομογραφία καρδιάς ενδεχομένως να καταστήσει μη απαρραίτητη την ενδομυοκαρδιακή βιοψία για την επιβεβαίωση διάγνωσης της νόσου. Επιπρόσθέτως με τη μαγνητική τομογραφία καρδιάς επιτυγχάνεται καλύτερη απεικόνιση ενδοκαρδιακών θρόμβων από ότι με τη διαθωρακική και τη διοισοφάγειο υπερηχογραφία.Οι ενδοκαρδιακοί θρόμβοι, συχνά απαντώμενοι στην ενδομυοκαρδιακή ίνωση, προκαλούν πνευμονικές ή συστηματικές εμβολές και αποτελούν μια από τις κύριες αιτίες θανάτου αυτών των ασθενών. Ο ακριβής εντοπισμός τους θα οδηγήσει σε έγκαιρη έναρξη αντιπηκτικής θεραπείας για αποφυγή αυτών των συμβάντων. Εκτός αυτού, σημαντικός είναι ο ρόλος της μαγνητικής τομογραφίας καρδιάς στην προεγχειρητική και μετεγχειρητική αξιολόγηση των ασθενών με ενδομυοκαρδιακή ίνωση που υποβάλονται σε ενδομυοκαρδεκτομή.Η εν λόγω απεικόνιση επιτρέπει προσεκτικό σχεδιασμό του χειρουργείου ενώ βοηθά το χειρουργό στην ορθή επιλογή της χειρουργικής προσέγγισης που θα ακολουθηθεί. Μετά την επέμβαση,η εν λόγω απεικονιστική μέθοδος βοηθά στην αξιολόγηση ανταπόκρισης των ασθενών στη χειρουργική θεραπεία καθώς και την ανίχνευση πιθανής υποτροπής της νόσου.

Στη νόσο Chagas ,με τη μαγνητική τομογραφία καρδιάς επιτυγχάνεται ποιοτική και ποσοτική αξιολόγηση της ίνωσης του μυοκαρδίου. Επιπροσθέτως απεικονίζονται με μεγάλη ακρίβεια τα ανευρύσματα κορυφής που απαντώνται συχνά στην χρόνια μορφή της νόσου. Μετά την ενδοφλέβια έγχυση σκιαγραφικού ,καθυστερημένος εμπλουτισμός εμφανίζεται συνηθέστερα στο υπενδοκάρδιο ή το υποεπικάρδιο του κατώτερου πλάγιου και κορυφαίου τοιχώματος. Οι περιοχές όπου παρατηρείται καθυστερημένος εμπλουτισμός συμπίπτουν με εκείνες όπου ανευρίσκονται τμηματικές διαταραχές κινητικότητας. Η μαγνητική τομογραφία καρδιάς μπορεί επίσης να συμβάλει στον υπολογισμό του κινδύνου εμφάνισης κακοηθών αρρυθμιών βοηθώντας στην επιλογή των ασθενών που αναμένεται να ωφεληθούν από την εμφύτευση απινιδωτή. Τέλος η

δυνατότητα την μαγνητικής τομογραφίας καρδιάς να ανιχνεύσει ενδοκοιλοτικούς θρόμβους συνεπικουρεί στην έγκαιρη έναρξη αντιπηκτικής αγωγής και πρόληψη καρδιοεμβολικών επεισοδίων και ισχαιμικών εγκεφαλικών που απαντώνται συχνά στη νόσο Chagas.

Η παρούσα εργασία αποτελεί μια συστηματική ανασκόπηση της βιβλιογραφίας πάνω στις ξεχασμένες μυοκαρδιοπάθειες δίνοντας έμφασης τις εφαρμογές τις μαγνητικής τομογραφίας καρδιάς στη έγκαιρη διάγνωση τους και διασαφήνιση της παθοφυσιολογίας τους. Γνωρίζουμε ότι οι ξεχασμένες μυοκαρδιοπάθειες πλήττουν ως επί το πλείστον ασθενείς χαμηλών κοινωνικοοικονομικών στρωμάτων, των οποίων η πρόσβαση σε μαγνητικό τομογράφο είναι περιορισμένη. Παρότι μοιάζει οξύμωρη, η επιλογή να ασχοληθούμε με την εφαρμογή μιας ακριβής εξέτασης του δυτικού κόσμου σε δυο παραμελημένες ασθένειες έγινε συνειδητά. Ο λόγος ήταν η ανάδειξη τρόπον τινά της ανισότητας απέναντι στη νόσο μεταξύ ανεπτυγμένου και αναπτυσσόμενου κόσμου και η αναγκαιότητα καθολικής προσβασιμότητας όλου του πληθυσμού σε πρώτης τάξεως υπηρεσίες υγείας.

Introduction:

Heart failure is a global pandemic with a huge economic burden for health systems(1). Nevertheless, the causes of this clinical syndrome are very different between industrial and developing countries. In Latin America and sub-Saharan Africa, two mysterious cardiovascular conditions are leading heart failure causes in populations of low socio-economic status. Chagas Disease(ChD) and Endomyocardial Fibrosis (EMF),the so-called forgotten cardiomyopathies, afflict approximately 8million and 12 million people respectively(2), yet the interest of the scientific community remains very restricted and effective treatment is missing.

ChD (or American Trypanosomiasis) is a parasitosis caused by the protozoan Trypanosoma Cruzi and transmitted to humans through hematophagous triatomine vector, endemic in the Americas(3,4).Carlos Chagas, a Brazilian physician, identified Trypanosoma as the causative agent and named it after his mentor Oswaldo Cruz(5).Approximately 30% of individuals infected by the causative agent develop the deadly chronic chagasic cardiomyopathy(CCC) characterized by high morbidity and mortality and poor prognosis. ChD is endemic in 21 Latin American countries and chagasic cardiomyopathy is the leading cause of infectious cardiomyopathy worldwide(6,7).

EMF was firstly described in 1948, when the Ugandan pathologist Jack Davies characterized it a distinct clinical entity(8). Endemic to the tropics with the vast majority of cases coming from Sub-Saharan Africa, it is the most common cause of restrictive cardiomyopathy worldwide(9). Mysteriously, large fibrotic plagues distributed typically at the apex and the subvalvular apparatus develop, causing restrictive physiology(10). Detecting these conditions, especially in early stage, remains a challenge, with misdiagnosis in non-endemic countries exceeding 95% for ChD (11,12).

Cardiac magnetic resonance(CMR) is a promising imaging modality which may help shed light on the insidious course of the neglected cardiomyopathies and reduce misdiagnosis rates. With better temporal and spatial resolution than echocardiography and the ability of tissue characterization, CMR plays a crucial role in the diagnosis, risk stratification, response to treatment monitoring and prognosis of various cardiovascular diseases.

The purpose of this manuscript is to raise awareness of the forgotten cardiomyopathies and outline the value of CMR in diagnosis and understanding of their natural course.

Methods:

Article search was conducted using the electronic database of Medline/Pubmed and Scielo using the following search terms: “Endomyocardial fibrosis/Sclerosis” OR “Chagas Disease” OR Restrictive cardiomyopathy AND “Epidemiology” or ”etiology” or “diagnosis” or “CMR” or MRI or” late gadolinium enhancement or ‘’tissue characterization” or”T1 mapping” or “”Extracellular volume fraction” (ECV).Equivalent terms in Spanish were used at the Scielo database. Articles in English French and Spanish were recruited. Key references, book chapters, reviews and patients reports were thoroughly reviewed. Finally, 138 articles were included in the review.

Endomyocardial Fibrosis:

Epidemiology:

EMF is a restrictive cardiomyopathy endemic to the tropics with the vast majority of cases coming from Sub-Saharan Africa. Nevertheless, large case series have been reported in the Kerala State of southern India, Brasil, Colombia and Ganxi province in China(13).Migration-related cases also appear in non-endemic European countries(14).Although EMF seems to be strongly related to poverty and social deprivation, Caucasian foreigners who immigrated to Sub-Saharan Africa also developed the condition thus making EMF epidemiology even more complex(15–17).

The frequency of EMF presents a bimodal distribution with first peak at age 10 and second peak among women of childbearing age(12,13,17,18).Discrepancy exists among studies on EMF sex preponderance. Males seem more commonly affected in Nigeria and Mozambique while Ugandan studies show higher rates among females(12,17). It seems to primarily affect the right ventricle(RVEMF) or both ventricles with left ventricular disease being more rare(19).

Epidemiologic data of the exact EMF prevalence are robust and regional variation of distribution has been depicted in different countries. Interestingly, a community-based study with 1063 individuals, conducted by Mocumbi et al. ,showed an overall EMF prevalence of 19,8% in the population of a rural area of Mozambique. Only 22,7% of those affected reported symptoms and increased frequency in family members was also found(20).

Another prospective cohort study compared the clinical manifestations, severity and survival between EMF patients from Trivandrum and Allepey district in Kerala State, India. Biventricular disease and incidence of atrial fibrillation (AF) was significantly higher in a region named Trivandrum compared to the Allepey region group of patients. Patients from Trivandrum also had much lower 6-year survival rates than Allepey(61% vs 91,5% respectively).The authors attribute their findings to malnutrition and lack of magnesium-rich foods (such as fish) from the diet of

Trivandrum residents. Absorption of the heavy metal cerium in the place of magnesium is thought to actively contribute to cardiotoxicity(21).

Etiology:

Various co-factors have been proposed to contribute to the development of EMF. Poverty, malnutrition, ethnicity, autoimmunity, dietary habits, toxic agents, infectious agents, hypereosinophilia and genetic susceptibility have been reported among others (22–24).

Increased occurrence of EMF between family members and among immigrants from Rwanda-Burundi residing in Uganda(12), raised the question of EMF predisposition and genetic susceptibility. Interestingly, Beaton et al. conducted HLA typing in EMF patients from Uganda and Mozambique and compared them with healthy controls.HLA-B58 and HLA-A*02:02 was significantly more frequent between EMF patients in Mozambique and Uganda respectively(24).

Hypereosinophilia seems to be a significant risk factor for EMF and eosinophil infiltration of the myocardium has been found to be inversely related to the chronicity of the condition(16). Immune stimulus-mediated eosinophil degranulation liberates major basic protein(MBP), eosinophil peroxidase(EPO) and eosinophil derived neurotoxin(EDN),substances with deleterious effects to the myocardial tissue(25,26) .After infiltration ,degranulation-induced necrosis occurs and thrombus formation follows possibly due to cationic proteins capability to bind thrombomodulin. Finally large fibrotic plagues involving the apex and the subvalvular apparatus are created(26,27).Fibrotic plagues of end-stage EMF seem to be identical to those observed in Loeffler's endocarditis, a disease endemic to temperate countries. The hypothesis that these two clinical entities represent the two extremes of the same disease triggered by eosinophil toxicity has been postulated(6,7,17,20). Malignancy or connective tissue disorders could be the eosinophilic trigger in Loeffler's while parasitic or protozoan infections, highly endemic in the tropics, could activate the eosinophilic cascade in EMF.

Indeed, various pathogens such as Microfilaria, helminthes, Plasmodium falciparum, Schistosoma, and Toxoplasma gondhi have been reported as possible causes of the disease in Sub-Saharan Africa(18).

In sharp contrast with the hypereosinophilia theory, other authors suggest a geochemical hypothesis to explain the cause of EMF. Monazite, an abundant mineral in EMF-afflicted countries

is rich in cerium and thorium. Increased levels of these toxic minerals in water and cassava tube crops, consumed by the locals, seem to play a role in the development of EMF(29). High concentrations of cerium and low levels of magnesium have been observed in the myocardium of EMF patients suggesting a cerium-magnesium antagonism in cardiac energetics (29,30). Animal data supporting the above hypothesis show the development of a cardiomyopathy similar to EMF in monkeys fed with a diet low in meat and fish and rich in cassava(16).

It is possible that EMF is the result of a complex interplay of a genetically susceptible person exposed to environmental triggers (dietary, eosinophilia, infections etc.). Nevertheless, its pathophysiology and etiology still remain an unsolved mystery and further research is pending to shed light on the subject and develop effective interventions.

Natural History and Clinical Manifestations:

Three phases of the disease have been described i) initial inflammatory phase ii)transitional indeterminate phase and iii) chronic fibrotic phase (31).

i) Patients at the initial phase of the disease usually appear with fever, periorbital edema, itching and urticaria. Hypereosinophilia has also been reported and peculiarly, circulating eosinophils are morphologically abnormal(31).Infiltration of the myocardium results to edema, wall thickening and development of mural thrombi in the apex or the subvalvular apparatus(32). Possibly due to limited access to health facilities from poor populations, the initial EMF phase is scarcely detected(12). Some patients rapidly deteriorate developing fulminant myocarditis and death while others have a slow progression of the disease with recurrent flare-ups(13).

ii) The indeterminate phase is characterized by recurrent inflammation relapse. Myocardial thickening and edema regresses and fibrotic tissue gradually develops in the affected areas. Factors contributing to the velocity of progression to chronic form remain obscure(31).

iii) As the disease progresses to the chronic phase, cachexia, hypoalbuminemia and malnutrition usually occur(12). Female sex secondary characteristics appear in male patients(32).Parotid swelling ,lips hyperpigmentation and central cyanosis in the absence of patent foramen ovale are sometimes present ,though the exact mechanism remains unknown(33).Cardiac involvement occurs in all patients. Fibrotic plagues develop with distribution in the apex and the subvalvular apparatus sparing the outflow tract. Subvalvular scar formation restricts tricuspid valve(TV) and mitral

valve(MV) mobility provoking malcoaptation and massive tricuspid regurgitation (TR) and mitral regurgitation(MR) respectively(34,35).Clinical manifestations mostly depend on the afflicted ventricle. Left ventricular EMF (LVEMF) presents with dyspnea and orthopnea. Cardiac auscultation reveals a soft systolic MR murmur and an increased pulmonary component of second tone attributed to elevated left atrial pressures(13).Contrarily, in right ventricular EMF(RVEMF), elevated systemic venous pressures provoke exophthalmos and congestive hepatosplenomegaly(36).Giant ascites without peripheral edema is typical of the disease but cannot be attributed to congestion solely(12,18).Ascitic fluid is exudative and cytology confirms lymphocyte presence and high protein content. It is believed that coexisting peritoneal inflammation mediates exudative ascitic fluid effusion. Fibrosis in skeletal muscles has also been observed in EMF patients. Ascitic fluid composition and peripheral muscle fibrosis both suggest the concept of EMF being an interstitial systematic condition with cardiac distribution rather than a cardiovascular disease(37).

Pulmonary hypertension is regularly detected in both forms of the disease. Severe diastolic dysfunction and retrograde increase of pulmonary pressures mediate the development of pulmonary hypertension in LVEMF. Contrarily in RVEMF, acute or chronic thromboembolism due to blood pooling seem to be the cause of pulmonary hypertension(36).

Massive pulmonary embolism, systemic emboli, arrhythmias and cirrhosis-induced hepatic failure are the main causes of death among others(31).

Diagnosis and imaging modalities:

X-Ray

Typically, chest radiograph in EMF is notable for increased cardiothoracic index, due to left, right or biatrial enlargement. Pericardial and/or pleural effusions are also a common finding(38). Endocardial calcification may appear but it is exceptionally rare(13).

ECG

ECG findings are not disease-specific.ST-T changes, low voltage QRS and atrial arrhythmias appear among others(39).In RVEMF , dominant R waves in V1 can be seen. Conduction disease may occur but pacemaker implantation is rarely required(12).

Echocardiography:

Increased echogenicity located at the apex and the subvalvular apparatus is frequently detected, a clue indicative of fibrosis. Engulfment of atrioventricular valve leaflets in scar tissue results in restricted motion and severe TR and/or MR(40). Filling pattern is characteristically restrictive with E/A>2, DT <160 msec, E/e'>14(41). Respiratory variation in MV and TV velocities is absent differentiating EMF from constrictive pericarditis. M-mode echocardiography of the septum and posterior wall can show square root sign. The apex is typically obliterated with fibrous tissue and thrombus in contrast with the hypercontractile base (Merlon sign). Massive biatrial enlargement with shrunken ventricles is also evident (35,42).

In 2008 a severity score and diagnostic criteria were developed for EMF. The presence of 2 major and 1 minor or 1 major and 2 minor criteria is considered diagnostic of EMF. Severity score <8, 8-15 and >15 is indicative of mild moderate and severe disease respectively(12). Echocardiography has a renowned position in the diagnosis of EMF .Advantages are low cost, availability even in endemic rural areas and portability. The main drawbacks of this imaging modality are limited acoustic window, inadequacy for tissue characterization, operator dependence and difficulty to differentiate between EMF and other conditions manifesting with obliterated apex(34,35).

Table 1
Criteria for assessment of the severity of endomyocardial fibrosis

Criterion	Score
Major Criteria	
Endomyocardial plaques >2 mm in thickness	2
Thin (<1 mm) endomyocardial patches affecting more than one ventricular wall	3
Obliteration of the right ventricular or left ventricular apex	4
Thrombi or spontaneous contrast without severe ventricular dysfunction	4
Retraction of the right ventricular apex (right ventricular apical notch)	4
Atrioventricular valve dysfunction owing to adhesion of the valvular apparatus to the ventricular wall	1–4[a]
Minor Criteria	
Thin endomyocardial patches localized to one ventricular wall	1
Restrictive flow pattern across mitral or tricuspid valves	2
Pulmonary valve diastolic opening	2
Diffuse thickening of the anterior mitral leaflet	1
Enlarged atrium with normal sized ventricle	2
M movement of the interventricular septum and flat posterior wall	1
Enhanced density of the moderator or other intraventricular bands	1

[a] The score is assigned according to the severity of atrioventricular regurgitation.
From Mocumbi AO, Ferreira MB, Sidi D, et al. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med 2008;359(1):46; with permission.

Differential diagnosis:

Distinction of EMF from other diseases can be challenging. Differential diagnosis must include constrictive pericarditis, rheumatic heart disease(RHD), Ebstein anomaly, apical hypertrophic cardiomyopathy (HCM) and other causes of restrictive cardiomyopathy such as amyloidosis, sarcoidosis,(8,13,18,42).

Signs present in RHD but not in EMF are: thickened valve leaflets, aortic valve involvement, evidence of mitral stenosis, absence of apical obliteration and normal or dilated ventricles(18,42).

Tuberculous constrictive pericarditis is quite common in EMF endemic countries and distinction between the two can be troublesome. In constrictive pericarditis, a respiratory variation pattern of the ventricular filling is characteristically seen with echocardiography. An increase of >25% in MV inflow E velocity during expiration and an increase of >40 % in TV inflow E velocity in inspiration support the diagnosis of constrictive pericarditis(43).Early diastolic mitral annulus velocity (e') is reduced in EMF contrarily to constrictive pericarditis where it remains

normal(44). Pericardial adhesions to the lateral wall in constrictive pericarditis induces reduction of e' lateral velocity to an extent that e' septal> e'lateral (annulus inversus).Thickened pericardium>4mm and ventricular septum shift are also present in constrictive pericarditis in contrast with EMF(45).When uncertainty still exists with echocardiography, CMR is the indicated imaging modality to differentiate between the two par excellence.

RV apical obliteration and an aneurysmal RA can suggest the diagnosis of Ebstein's anomaly. Nevertheless, abnormal TV leaflet coaptation and involvement of the outflow tract differentiate Ebstein anomaly from EMF(42).

In amyloidosis, diffuse myocardial hypertrophy, thickness of interatrial septum and absence of apical thrombi can help the discrimination from EMF with echocardiography. Nevertheless the gold standard to differentiate between the two is CMR(35).

Apical obliteration in systole is the hallmark to distinguish between apical HCM and EMF. In EMF the apex remains obliterated during all the cardiac cycle(35).

Treatment:

In analogy with Loeffler's endocarditis treatment, corticosteroids and immunosuppressants could improve outcome in early forms of EMF(13).Interestingly, increased levels of IL-6 have been observed in patients with recent onset EMF. Whether anti-IL6 monoclonal antibodies such as tocilizumab- a drug used in rheumatoid arthritis- could be efficient in EMF, remains a field for future research(8,46).

Administration of oral corticosteroids is often considered but randomized clinical trials to ascertain their efficacy in EMF heart disease are still an unmet need. A randomized placebo-controlled double blind clinical trial conducted by Nabunnya et al., questioned the efficacy and safety of prednisolone to prevent ascites reaccumulation in patients with advanced stage EMF. Disappointingly, after 8 weeks follow-up, prednisolone failed to prevent fluid reaccumulation(47).

Standard heart failure treatment is given to relieve symptoms in patients with EMF. B-blockers, angiotensin converting enzyme inhibitors(ACEIs),angiotensin receptor blockers(ARBs) and diuretics are used among others. Spironolactone, known for its antifibrotic effects and capability to improve outcome in HF patients is often preferred from other diuretics(48).AF in EMF is cardioversion-resistant and is thus managed with rate control. Patients with AF also receive oral anticoagulants for thromboembolism prevention(8,49).

Although technically difficult and inaccessible in many endemic areas, surgery seems to improve survival in EMF patients compared to medical therapy(50).Individuals with EMF and NYHA III-IV class symptoms without irreversible hepatic or cardiac lesions are good candidates for operation(50,51). Contraindications include chronic pulmonary thromboembolic disease, cachexia, severe ascites, extensive fibrosis and leaflet shortening(18).Perioperative mortality rate is approximately 20% with low cardiac output syndrome and complete heart block being the leading causae mortis(34,52). Endocardectomy –careful excision of the fibrotic endocardium- and atrioventricular valve repair or replacement is the preferred surgical procedure. Removal of thrombi from the apex or the left atrial appendage, liberation of papillary muscles and chordae tendinae engulfed in scar tissue is regularly performed (18). In cases where the atrioventricular valve involved cannot be repaired, bioprosthesis is preferred from mechanical valve due to anticoagulation issues(31).Individuals with severe RVEMF may benefit from cavopulmonary anastomosis and 1,5 ventricle procedure(13,18).

B. Chagas Disease:

Epidemiology and Etiology:

Strongly correlated with poverty, causing a remarkable economic, social and human burden, ChD was characterized by WHO as a neglected tropical disease (53,54). ChD is a zooanthroponosis caused by the protozoa Trypanosoma Cruzi, primarily affecting sylvatic rural areas of the Amazon basin. In endemic areas, the pathogen can be transmitted to humans through the bite of a triatomine vector bug residing in local traditional housing settlements. Deforestation of tropical rainforests and extinction of wild mammals , being major food source for triatomines seems to be the main cause of vector immigration to peridomestic settings(3,54). Alternative non-vectorial transmission pathways are i) infected blood transfusion, ii) organ transplantation ,iii) vertical transmission from mother to fetus, iv) oral transmission via contamination of infected food or beverage(6,54). Symptoms of the acute infection are either absent or mild in the majority of cases but 30% of those infected will develop the deadly chronic chagasic cardiomyopathy (CCC)(55).

In previous decades, multinational initiatives targeted to minimize vectorial and eradicate transfusion-related transmission, were launched in countries of the Southern Cone ,the Andes, Central America and the Amazon basin (5,54).In 1999, after successful completion of these programs, the Pan-American Health Association (PAHO) declared T.infestans (triatominae vector) ,eradication from domestic areas in Brazil, Uruguay and Chile. Epidemic surveillance is of critical importance as the Bolivian Gran Chaco region, Brazil, southern Peru, southern Mexico, Nicaragua , Ecuador and el Salvador remain highly endemic (39).

Noteworthy progress has been marked in blood products screening with 12 Latin American countries achieving the goal of 100% coverage and 2 countries accomplishing 99%. Worryingly, Bolivia has the highest ChD prevalence worldwide but its blood donor screening coverage rates do not exceed 80%(56).Oral transmission via consumption of contaminated fruit juices or vegetables is possible with 768 cases reported in Latin America between 2004 and 2013 (7,57).Congenital transmission prevalence is 15000 ChD cases per year. High maternal parasitemia level, parasite placenta-invading capability and maternal or neonate immunodeficiency seem to be significant co-factors(58).

Immigration of infected individuals radically changed the epidemiology of ChD subserving its expansion to non-endemic countries where the disease is transmitted through non-vectorial pathways such as organ transplantation, blood transfusion or vertically (53)(59).A systematic review and meta-analysis of 18 studies conducted in Italy, Switzerland, France, Germany and Switzerland calculated a 4.2% pooled prevalence of chronic ChD infection in LA immigrants living in Europe (95%CI :2.2-6.7%), p<o.o1).According to literature, 300000, 122000 and 10000 ChD cases live in USA, Europe and other non- endemic countries respectively(6,56,57).European data indicate highest prevalence of ChD in Spain Italy and the UK (59)while misdiagnosis rate in the old continent exceeds 95%(60).

Natural History-Pathogenesis:

After parasite inoculation, an incubation period of 1-2 weeks follows before manifestation of acute infection symptoms(61,62).The duration of the acute phase is 2-3 months and after its completion 70-75% of infected individuals enter the indeterminate form of ChD(62). One or two decades later, 25-30% of seropositive individuals eventually develop chronic ChD : CCC and/or gastrointestinal ChD(11).

ChD pathogenesis and the ways the infectious agent elicits myocardial damage is a field yet remaining elusive(55). Trypanosoma- induced neuronal depopulation, autoimmunity , parasite persistence coronary microvascular abnormalities and oxidative stress seem to play a critical role(54,61,63).TGF-β, GM-CSF , Galectin-3 and a variety of other molecules produced by the inflammatory cascade seem to mediate fibrosis and myocardial cells hypertrophy. Moreover, the production of Th1 cytokines and the presence of T.cells recognizing cardiac myosin also correlate with severe myocardial damage(55).

Clinical manifestations:

i)Acute ChD

Acute ChD infection is an asymptomatic or mild febrile illness. In vectorial transmission cases, myalgias, sweating, diarrhea, vomiting, lymphadenopathy and facial/limb edema occur(6,53,61) .A minority of cases may present with inflammation nodules at the site of inoculation called Chagomas. Periorbital edema appears in cases of Trypanosoma invasion through the conjunctiva(Romaña sign) (54,61).Oral transmission is correlated with more serious acute ChD with painful abdomen, hemorrhagic jaundice and splenomegaly. Chagomas and Romaña sign are characteristically absent in this form(53). Independently of transmission mode, fulminant myocarditis, pericardial effusion and/or encephalomyelitis occur in 1% of infected individuals leading to fatal outcome(55,60,62).Differential diagnosis of acute ChD includes leptospirosis, hepatitis, dengue fever and hantavirus infection(64). Electrocardiographic findings of the acute phase are sinus tachycardia, PR and/or QT prolongation, low voltage, ST-T changes(61,62).The above findings resolve after the acute phase(64).

ii) Indeterminate phase:

After the acute phase resolves the majority of those infected pass to the indeterminate form of ChD This phase is characterized by: normal clinical examination, normal ECG and normal chest,

radiograph in an asymptomatic person serologically positive for T. Cruzi (65).Transition rate from the indeterminate to the chronic form of ChD is thought to be approximately 5% per year(66). Surprisingly, despite being clinically silent, histopathological changes such as edema, myocardial infiltration and fibrotic lesions can be observed in cardiac biopsy of patients with indeterminate ChD(67). Decreased chronotropic response to exercise, diastolic dysfunction and decreased velocities of circumferential shortening in the LV have also been described(67).

iii) Chronic Chagasic Cardiomyopathy:

CCC eventually develops in 30 % of initially infected cases presenting with three clinical syndromes: i)arrhythmogenic syndrome, ii)thromboembolism/stroke, iii)heart failure (54,56).CCC combines characteristics of both the dilated and arrhythmogenic cardiomyopathy rendering its diagnosis and management a clinical challenge. Clinical stages of CCC according to Andrade et al. are: A: no heart failure symptoms, no structural cardiac disease, B: structural heart disease without HF symptoms, B1: ECG alterations with or without the presence of echocardiographic findings without the presence of ventricular dysfunction, B2: reduced LVEF due to ventricular dysfunction, C: LV dysfunction accompanied by HF symptoms (NYHA I-IV),D: end –stage therapy-resistant HF (NYHA IV)(68).

-Arrhythmogenic syndrome:

Clinical presentation of the arrhythmogenic syndrome in CCC, is variable with tachy- and brady- arrhythmias of atrial and ventricular origin composing the clinical spectrum. Sinus node dysfunction, sinus bradycardia , 2^{nd} or 3^{rd} degree A-V block ,left bundle branch block(LBBB), monomorhic or polymorphic premature ventricular contractions(PVCs) and malignant ventricular arrhythmias regularly occur to name a few(69,70).

Bradyarrhythmias:

Fibrosis is thought to be a major cause of conduction disease in CCC. Scar formation insults the sinus node, A-V node and His bundle manifesting as sick sinus syndrome and A-V blocks(71). Sick sinus clinical spectrum includes bradycardia episodes, sinus pauses, sinoatrial block and tachy-brady syndrome. Pacemaker implantation and permanent pacing is often necessary in CCC

patients(72).Advanced degree atrioventricular blocks (2^{nd},$3^{rd)}$ and bundle brunch blocks also orchestrate the conduction disease in CCC. RBBB+ LAFB pattern in resting ECG is suggestive of ChD and should arouse suspicion for laboratory testing especially in endemic settings(73).

Atrial tachyarrhythmias:

Detected in more than 5% of individuals with CCC, AF predicts mortality and constitutes a risk factor for stroke independently of LVEF(74–76). AF prevalence in ChD cardiomyopathy is a field of conflicting results. Although increased prevalence of the arrhythmia has been associated with CCC in previous studies, a meta-analysis of 3282 patients with cardiomyopathy did not show differences in AF prevalence between patients with chagasic and non-chagasic cardiomyopathy(77). AF prevalence in patients with heart failure of chagasic and non-chagasic etiology was compared in a meta-analysis of 7 studies including 1974 persons but no statistical importance was observed either(p=0.55), suggesting that AF prevalence in chagasic and non chagasic cardiomyopathy do not seem to differ(77).

Ventricular tachyarrhythmias:

Ventricular arrhythmias, common in ChD , correlate with high rates of morbimortality and may explain the worse prognosis of CCC compared to primary dilated cardiomyopathy patients(78). Monomorhic/polymorphic PVCs, ventricular couplets and runs of NSVT are frequently observed on ECG. Polymorphic PVCs NSVT and VT are independent high risk factors for sudden cardiac death (SCD) (79). Complex ventricular tachyarrhythmias seem to correlate with the severity of regional wall motion abnormalities but they may occur even in patients with preserved left ventricular ejection fraction LVEF(80,81). SCD happens between 30 and 50 years of age and ventricular fibrillation (VF) seems to be its major determinant(80).

The formation of the arrhythmogenic substrate in CCC is a multifactorial condition. Inflammation-induced myocardial fibrosis and microvascular perfusion deficits contribute. Scar tissue seriously damages the intercellular junctions causing stimuli conduction delay ,thus prospering the formation of a re-entrant circuit (82). According to literature ,the predilection of fibrosis pattern for the LV inferolateral wall renders it the most common focus of VT in chagasic cardiomyopathy(53,71).Fibrosis quantification assessed with LGE-CMR is a cutting-edge promising technology to identify high risk patients(71).

Thromboembolism/Stroke:

Cerebrovascular events may develop in the progress of ChD frequently leading to fatal outcome. Cardioembolism-induced strokes, routinely offend younger ages and may be the first manifestation of CCC(83,84). Factors predisposing to stroke in CCC, are intracardiac thrombi, left atrial enlargement, apical aneurysm, LV dysfunction and atrial fibrillation(71,84).

Interestingly Cardoso et al. in a meta-analysis of 8 studies and 4158 patients, demonstrated an elevated Odds Ratio for the occurrence of stroke in ChD especially in individuals with CCC($p=0.04$). This correlation of CCC with stroke opens an interesting conversation regarding its role in mortality risk assessment(85).

Currently, mortality risk evaluation in CCC is based on Rassi score(86). Independent factors that predict mortality according to Rassi et al are: NYHAIII or IV(5 points), cardiomegaly on chest radiograph(5 points)segmental or global wall motion abnormalities(3 points),NSVT(3 points), low QRS voltage(2 points) and male sex(2 points). Thus, chagasic patients are classified into 3 groups: low risk (0-6 points), intermediate risk (7-11 points) and high risk(12-20 points). Respective mortalities are 10%,44% and 84% after a decade follow-up(80,86). However, Rassi score does not take into account cerebrovascular events in chagasic patients and supplementary research should be conducted to evaluate the possible prognostic value of stroke in mortality risk calculation.

Heart failure:

ChD gradually progresses to dilated cardiomyopathy resulting in heart failure. In sharp contrast to primary dilated cardiomyopathy, CCC frequently presents with right heart failure signs and symptoms: hepatomegaly, ascites and peripheral edema are quite common. Left-heart failure symptoms such as dyspnea on exertion, loss of consciousness, and weakness also occur(54,61,63).

Diagnosis and imaging modalities:

Laboratory testing:

During the acute phase of the disease, trypanomastigotes can be viewed through microscopic examination of the blood and set the diagnosis of ChD(87–90). However, once the disease proceeds to the indeterminate or the chronic form, evident parasitemia is non-detectable and serological tests such as enzyme-linked immunoabsorbent assay, indirect immunofuorescence(ELISA), immunochromatography and indirect hemagglutination are recommended(91).These tests detect anti-T.Cruzi IgG but have supoptimal sensitivity and specificity. Positive results from two different serological tests are demanded in order for ChD diagnosis to be confirmed(92). PCR can also diagnose ChD but is not the preferred diagnostic test in clinical practice due to lower sensitivity and higher cost than serological tests(91).

X-ray:

Cardiomegaly with or without pulmonary venous congestion can be seen in chest radiograph being a powerful indicator of ominous prognosis.(69) In the acute phase, x-ray can help estimate the extent of pericardial effusion. Moreover in patients with a normal ECG and confirmed ChD infection a normal chest radiograph is necessary to classify them in the indeterminate form of ChD(65).

ECG:

No pathognomonic ECG finding exists for CCC to date. However, the coexistence of right bundle branch block(RBBB) with left anterior fascicular block (LAFB) in resting ECG is highly suggestive of CCC. Interestingly, recent meta-analysis data suggest that CCC patients have a 5-fold increase in the odds of having RBBB+LAFB ECG pattern compared to non ChD patients with cardiomyopathy(OR= 5.31, CI:1.23-22.86 P=0.03).Positive prognostic value and specificity for the diagnosis of CCC in patients with this ECG pattern was 92% and 99% respectively(77).Consequently, this finding ,combined with compatible patient epidemiological

background, should arouse suspicion of CCC and prompt diagnostic testing. LBBB, although less common is related with worse prognosis(79).

Echocardiography:

In patients with CCC the most common echocardiographic findings are pericardial effusion, regional wall motion abnormalities and globally reduced LVEF. Ventricular aneurysms, typically located at the LV apex, participate in the clinical spectrum(69).Independently predicting the development of thrombi and stroke, aneurysms occur in 8% of asymptomatic cases and in 47-64% of cases with moderate to severe cardiac impairment. Gradual chamber dilatation as the disease progresses results in functional MR and/or TR(93).Wall motion abnormalities characteristically have a predilection for the inderolateral wall and the apex(71).
Among echocardiographic parameters, LVEF is the most important independent predictor of mortality and should be carefully assessed using Simpson's biplane method or 3D echocardiography when available.

Diastolic dysfunction precedes systolic dysfunction in CCC course(75,88). Patients with recent onset of HF symptoms present with already advanced Grade II/III diastolic dysfunction .Interestingly, an E/e' ratio>15 strongly predicts poor outcome in CCC and is correlated with BNP levels, NYHA functional class and detection of fibrosis in LGE-CMR(94).

Challenging to evaluate with echocardiography the RV involvement in CCC can be insidious correlating with pulmonary hypertension (95) and an ominous prognosis(78,93). In some cases, RV apically located aneurysms can be the only echocardiographic finding indicating RV involvement in ChD. Moreover, early in the course of ChD and in absence of LV dysfunction, gradual scar formation in the RV may be a significant arrhythmogenic focus increasing the risk of sudden death. In patients without LV impairment, RV scar quantification with CMR is the gold standard to assess the arrhythmic risk(80).

Chagasic cardiomyopathy HF treatment:

HF management optimization in CCC is a field for future research as adequate clinical trials are pending. In the absence of CCC-specific guidelines, management of HF in these patients is based on non-ischemic HF treatment instructions(53).

Standard therapy of chagasic HF includes blockade of the renin –angiotensin system with ACEIs and ARBs(53,69,82). When kidney failure or hyperkalemia and CCC co-exist, replacement of ACEIs/ARBs by hydralazine and isosorbite nitrate is indicated(53).

Beta-blockers seem to enhance clinical status and have been correlated with lower mortality and increased survival(71,96,97). Their use in CCC has been controversial due to bradycardia, hypotension and A-V blocks perceived risk (69,82). Interestingly a randomized, placebo-controlled, double-blind clinical trial on carvedilol use was conducted by Botoni et.al. Results showed safe carvedilol use and no correlation with bradycardia events (96,98). Metoprolol and bisoprolol also constitute safe alternatives(53).Consequently, unless contraindication exists, b-blockade in symptomatic CCC is recommended and should be encouraged.

In NYHA III/IV patients, treatment with potassium-sparing diuretics such as spironolactone or eplerenone should be given in order to improve survival(53,69). Digoxin and diuretics do not seem to influence outcome in CCC and are used for symptoms improvement in patients not responding to standard therapy after maximal titration(53).Digoxin enhances exercise capacity but its administration is contraindicated in patients with A-V blockade ,beta blockade or receiving amiodarone(82).

Anticoagulation is indicated in all patients with paroxysmal or permanent AF, cardiac thrombi or embolic events(68). Individuals with apical aneurysms may also benefit from anticoagulants(99).

Heart transplantation should be considered in end-stage HF or when dependence on inotropes occurs(69). Notwithstanding that CCC has worse prognosis than other cardiomyopathies, graft recipients with CCC tend to have better survival rates compared to non-CCC recipients(53,69). Nevertheless, post-transplantation treatment with immunosuppressive drugs may reactivate ChD(100).

Stem cell therapy with bone marrow mononuclear cells (BMMCs) and mesenchymal stem cells(MSCs) has been tested as a therapeutic strategy for CCC. Injection of BMMCs and MSCs in the coronary arteries was efficient in animal models but results in humans have been disappointing(101).

Chagasic cardiomyopathy arrhythmias treatment:

Polymorphic PVCs, NSVT and VT require antiarrhythmic therapy especially in patients with decreased LVEF(102).Amiodarone, well-known for its antiarrhythmic properties and safety profile, is a first-line agent against arrhythmias in CCC. Interestingly, a direct antiparasitic activity of the drug has also been reported(92). Meta-analysis data suggest amiodarone effectively reduces SCD incidence (p=0.01) and cardiovascular death(p=0.04) but failed to alter all-cause mortality(79,103). Indications for its use are: individuals with impaired LVEF and symptomatic NSVT, patients with LGE in CMR, presence of late potentials in Signal-Averaged-ECG, T wave variability and patients with implantable cardioverter defibrillator (ICD) implanted to reduce inappropriate shocks(71).Amiodarone major side effects include bradyarrhythmias, thyroid toxicity, corneal deposits and pulmonary interstitial disease among others(69).

In patients presenting with VT events or resuscitated after SCD, pharmacologic treatment is insufficient and implantation of an ICD should be considered as a secondary prevention measure(53).Guidelines suggest that individuals with non-ischemic dilated cardiomyopathy with LVEF≤35% and NYHA II or III functional class are candidates for ICD implantation. Clinical trials to evaluate the applicability of these recommendation to CCC are still pending(69).

In a large observational study with 90 CCC patients bearing ICD for secondary prevention, Cardinalli-Neto et al. analyzed mortality rates. After 1,2,3,4 and 5 years follow-up mortalities were 18%, 27%, 40% 50% and 73% respectively. Number of shocks delivered within the first month of follow-up was the only determinant of all-cause mortality (p=0.05)(96,104).

ICD implantation as a primary prevention measure in CCC patients has been proposed by some research groups. Results from the “CHAGASICS Trial”, investigating ICD implantation supremacy over antiarrhythmic therapy for primary prevention of SCD in CCC, are expected to shed light on the subject (105). Nevertheless, the cost-effectiveness of ICD implantation as primary prevention in CCC, is an issue for many Latin American fragile economies(69).

Arrhythmic risk assessment in CCC is more challenging than other non-chagasic cardiomyopathies as in CCC, ventricular arrhythmias sometimes precede LV dysfunction development(79). RV scar formation, unrecognizable in echocardiography, and dysautonomia, seem to actively contribute to this phenomenon. Scar quantification with CMR is anticipated to bring revolutionary changes in the risk-stratification of these patients(78,80).

Epicardial ablation may be considered in the following occasions: i) symptomatic monomorhic VT recurring after full antiarrhythmic treatment or when antiarrhythmics are not desired or tolerated, ii) VT storm without reversible transient etiology, interfascicular or bundle-branch reentrant VT, iv) polymorphic drug resistant VT or VF when specific trigger is suspected(106).

Bradyarrhythmias occurring in CCC should be treated according to non-ischemic dilated cardiomyopathy instructions. Pacemaker implantation is recommended in cases of sick sinus syndrome and A-V block(69).

Anti-parasitic treatment:

Current anti-trypanosomal drugs available are beznidazole and nifurtimox (87–90). Both drugs exploit trypanosomal vulnerability to free radicals. Beznidazole provokes T.Cruzi DNA destruction by inducing free radicals production while nifurtimox acts by inhibiting a trypanosomal enzyme responsible for detoxification of such metabolites(91). Antiparasitic treatment is indicated in all acute ChD infections independently of transmission route (88,90). Patients<40 years old in the indeterminate form of the disease also seem to benefit (107). Cure rates range from 60 to 90 % of acute ChD cases and 10-20% of chronic infections. Interestingly children with acute congenital infection seem to have better treatment outcomes with respective curative rate being >90% and better tolerance compared to adults(91,108).

Unfortunately available treatments have major side effects such as erythema, peripheral neuritis, pruritic rash, anorexia, gastrointestinal symptoms and ,in rare cases, severe agranulocytosis. Twenty-one days after the initiation of beznidazole ,a general blood count exam is recommended to assess for leukopenia(71). The recommended dosage for beznidazole is 10mg/kg/day in cases of acute infection or 2.5mg/kg/12hrs for 2 months in chronic ChD infection(69). Respective dose for nifurtimox is 10mg/kg/day for 2 months in adults and 15mg/kg/day in children(53) .Prescription in pregnancy is contraindicated and alcohol use during treatment must be avoided(53)

Another issue of available drugs is failure to modify clinical outcome in patients with cardiomyopathy. The BENEFIT trial was the first placebo-controlled randomized clinical trial evaluating the efficacy of beznidazole vs. placebo in CCC(109).Disappointingly, patients receiving beznidazole for 2 months and followed for 5 years did not benefit from treatment compared to placebo(89,109).Treatment achieved significant reduction of parasite load but failed to halt the

progress of CCC (53). Consequently antiparasitic treatment in patients with established CCC should be discouraged.

The present manuscript urges the need for new safer and more efficient anti-trypanosomal drugs fabrication. International organizations should also guarantee drug availability in stranded endemic areas of Latin American countries with restricted economic resources.

Screening prevention and public health:

Public health measures taken in the previous decades actively reduced ChD prevalence in endemic areas(91).Housing improvements, insecticides use and blood donor screening programs constituted the pillars of the eradication programs implemented(102).

However, globalization, unemployment and poverty in Latin America account for the immigration of LA migrants and the expansion of ChD in non-endemic countries(88).Despite that more than 400000 cases are calculated to live outside Latin America ,ChD still remains neglected with misdiagnosis rates in Europe touching 95%(59,60,91). In countries with large numbers of Latin American migrants, educational programs on ChD for health care workers could be applied to increase awareness(89,91).

Blood banks screening for ChD is of major importance in non-endemic areas. Spain and France are the only European countries that perform blood transfusion testing for ChD. The United Kingdom and Italy exclude people of Latin American origin from blood donation(110).

Significantly increasing neonates morbidity and mortality, congenital ChD pooled transmission rate in non-endemic countries was calculated 2.7%(111). In an attempt to restrict congenital transmission, screening programs to detect pregnant women of Latin American origin in Europe are conducted in Tuscany and Bergamo(Italy), Valencia and Catalonia(Spain) and at the Geneva University Hospital(Switzerland). Other countries such as the USA, Canada, New Zealand and Japan have received great numbers of South American migrants in their territories but congenital ChD prevalence in these states is unknown and no screening programs exist(111).Serological screening of LA migrants(primary prevention),anti-parasitic treatment of

infected mothers(secondary prevention) and infected new-borns (tertiary prevention) could effectively help eradicate congenital transmission(91).

Vaccine development would be a hallmark in ChD prevention but no great progress has been marked on the subject. To note, living vaccines may be dangerous and killed ones may not be efficient in preventing ChD (89).

Interestingly, recent research assessed the cost-effectiveness of screening asymptomatic LA migrants living in western Europe for ChD in primary health centers. According to this study by Mendez et al, active screening of these people in primary health-care centers and treating seropositive persons with anti-parasitic drugs, is cost-effective and should be encouraged(112).

C. The promising role of CMR

CMR characteristics:

Cardiac Magnetic Resonance (CMR) has made major inroads in the diagnosis and risk-stratification of patients suffering from cardiomyopathy. Important information provided from CMR, facilitates the assessment of cardiac anatomy, function perfusion and viability in a "single window environment"(113).Chamber size and RV or LV ejection fraction are accurately quantified par excellence but what distinguishes CMR among cardiac imaging modalities is the ability of tissue characterization. Late gadolinium enhancement(LGE), T1 mapping and T2 mapping constitute the main tissue tracking approaches with the potential of detecting and quantitating diffuse fibrosis(114).Validated against biopsy in many clinical settings, these techniques have great perspective to elucidate the natural course, reduce misdiagnosis rates and guide treatment of the neglected cardiomyopathies.

Standard SCMR protocol for non-ischemic cardiomyopathy is used ,as disease-specific recommendations both for ChD and EMF are currently lacking(35,115).Single-shot free precession(SSFP) cine images are generated to assess LV segmental and global function and provide information on flow. Standard views include basal short axis(SAX), mid-SAX ,apical-SAX , 4-chamber,3-chamber and 2 –chamber. Additional views of the left ventricular outflow tract(LVOT) and RV(potentially of critical importance both in ChD and EMF) can be obtained(115). Characterized by high signal to noise ratio (SNR) and good contrast between blood

pool and myocardium, SSFP cine images have been proposed as an alternative to conventional echocardiography(113).

Detection of local fibrosis can be achieved by intravenous administration of gadolinium-based contrast agents(GBCAs) and the late gadolinium enhancement technique(LGE). In the course of this technique, MRI images are acquired approximately 15 minutes after the injection of GBCA. A preparatory inversion recovery radiofrequency pulse is used to null the normal myocardium before image acquisition(116). Delayed gadolinium washout in regions with fibrosis, inflammation or infiltration compared to normal myocardium, results in hyperintense signal in MRI T1 weighted images(117).Geographical distribution of delayed enhancement in different myocardial layers(subendocardial, midwall, subepicardial) and myocardial walls arouses suspicion of different cardiac conditions facilitating differential diagnosis(118).Drawbacks of LGE technique include gadolinium toxicity issues especially in patients with renal impairment. Although relatively rare, allergic reactions, renal failure and nephrogenic systemic fibrosis have been reported among others(119).Importantly, apart from restrictedly used in patients with renal impairment, the main limitation of LGE technique is its incapability to quantitate scar and its suboptimality to detect interstitial diffuse fibrosis ,prominent in early stages of cardiomyopathy(117).

In pursuit of tissue characterization and diffuse fibrosis quantification with CMR, T1 and T2 mapping, two novel imaging techniques showing clinical promise have been developed(120). The main concept of this technique is measuring T1 and T2 relaxation times of tissues after disturbing the equilibrium with a radiofrequency pulse(121).Non-contrast native T1 and T2 values, specific for each tissue, are calculated contributing in detection of myocardial pathologies. Diffuse interstitial fibrosis, inflammation, edema and infiltration have all been reported to significantly alter T1 times of the myocardium while T2 values are mainly influenced by increased myocardial water (edema etc)(122). Color encoded T1 maps are generated using the Look-Locker, MOLLI, shMOLLI or SASHA sequences(121–123).After GBCA injection, the extracellular volume (ECV) can be calculated measuring the T1 values of blood pool and myocardium before and after contrast injection and correcting for the hematocrit level.

Unfortunately, T1/T2 mapping have not been tested in the clinical context of ChD or EMF but they may help us illuminate their pathogenesis. In particular, authors suggest that native T1 mapping attained to distinguish acute from convalescent myocarditis and was superior to LGE in diagnosing this condition(122).Furthermore, T2 mapping is used to detect and quantitate myocardial edema in acute myocarditis(124). Myocarditis is thought to be a key feature in the

natural course of both the neglected cardiomyopathies(13,55).Hopefully, these exciting advances in CMR imaging may increase our understanding about the recurrent myocarditis flare-ups in ChD and the fulminant myocarditis episodes reported in both ChD and EMF(13,55).

EMF CMR findings:

In cine SSFP images massive biatrial enlargement with shrunken ventricles and pericardial effusion is regularly observed. LVEF, RVEF, mildly impaired in EMF, are accurately calculated. (125,126).

Subendocardial hyperenhancement without coronary distribution located at the apex and the inflow tract, characteristically sparing the outflow tract are the typical findings after injection of contrast in EMF(35,125–127). Interestingly, a three-layered appearance of the cardiac apex with hypointense normal myocardium, thickened fibrotic endomyocardium and overlying hypointense apical thrombus/calcification -the so called double V sign- has been described in literature and should be considered a typical finding(128). A single V sign with subendocardial LGE of the apex in the absence of apical thrombus may also be found(35,125). Carneiro et al. ,in a retrospective study of 44 EMF patients examined with CMR, found that 89% of patients presented with an apical LGE pattern. From those, double V sign and single V sign was present in 54% and 28% of cases respectively(129).

Clinical applications:

CMR is an imaging modality with various applications in the diagnosis and management of EMF. Researchers have proposed that CMR could replace endomyocardial biopsy conducted during surgery or cardiac catheterization for diagnostic purposes (35). Endomyocardial biopsy, an invasive procedure not spared of complications, has been used as a diagnostic method for EMF, yet its role remains controversial(18,130). Interestingly, Salemi et al demonstrated excellent correlation of the delayed enhancement V sign observed in CMR with scar tissue detected in biopsy specimens obtained intra-operatively(35,116).Hence, we can assume that in the near future, endomyocardial biopsy may not be necessary in EMF patients with typical delayed enhancement pattern in CMR. According to literature, a possible value of delayed enhanced CMR in guiding endomyocardial biopsy optimizing its diagnostic potential has been proposed. Nevertheless, in a multicenter study no significant differences in the number of positive biopsies was observed when related to the regions of hyperenhancement suggesting preferential biopsy being of no incremental value(131).

Taking into consideration that systemic and pulmonary embolization constitute important causes of death in EMF(31), early diagnosis of intracavitary thrombi, is an imperative need to prevent fatal outcomes. The diagnostic value of CMR has been demonstrated in this clinical scenario outperforming transthoracic and transesophageal echocardiography. In a retrospective study of 361 patients with confirmed LV thrombus, contrast-enhanced CMR was shown to be highly sensitive and specific for the diagnosis (88+/- 9% and 99+/- 2% respectively) surpassing both TTE and TEE(132). Detection of hypointense intracavitary filling defects adjacent to hyperintense fibrotic areas is highly suggestive of thrombus in delayed enhanced CMR(132,133).Thrombus chronicity and coexistence of calcification can also be specified(116).Having knowledge of the presence of thrombi in EMF patients, is an important clue both for clinical cardiologists to start anticoagulation and for surgeons performing endocardectomy.

Endocardectomy is a technically difficult procedure including careful resection of scar tissue from the endocardium. Superior to medical therapy, it seems to improve survival in NYHA III/IV EMF patients(50). Pre-operative evaluation of surgery candidates with CMR, offers unique anatomical details permitting careful surgery planning. Identification of fibrotic loci preoperatively guides the surgical approach. Specifically, extensive apical calcification detected in CMR is of vital importance and may alter the surgical approach followed(116).Aside from surgery planning ,CMR can actively contribute to post-operative evaluation of EMF patients. Accurate quantification of ejection fraction, ventricular volumes and mass, render CMR an appealing tool to monitor response to surgical treatment. In addition, EMF recurrence after operation could be detected in early stages.

Chagas CMR findings:

CMR imaging in CCC can excellently assess cardiac anatomy and function allowing for quantitative and qualitative assessment of myocardial fibrosis. Moreover, the apical aneurysms commonly found in CCC, can be excellently visualized in cine SSFP images outperforming echocardiography were the acoustic window can be limited(71). After the injection of GBCA various LGE patterns are observed. In particular the LGE pattern in ChD may be subendocardial, supepicardial, midwall or transmural(134).Interestingly its geographical distribution commonly occurs at the apical or the inferolateral walls, coinciding with the predilection of regional wall motion abnormalities for these myocardial segments(67,71).

Clinical applications:

It has already been validated that fibrotic lesions constitute the main arrhythmogenic substrate in CCC(71). Myocardial areas with perfusion deficits or regional wall motion abnormalities often coincide with foci of ventricular tachycardia(135). Moreover, recent research data has demonstrated a correlation between the amount of myocardial fibrosis and the Rassi severity score and a significantly higher percentage of myocardial fibrosis in patients with CCC presenting arrhythmic events(136).Hence, CMR , with its unique potential of tissue characterization can accurately quantitate scar tissue and facilitate the risk-stratification of patients with CCC at high arrhythmic risk(71) and potentially detect those who would benefit from an ICD.

Apart from identifying high-risk patients with ChD, CMR can also guide decisions on the pharmaceutical therapy of arrhythmias in CCC. In particular, CMR-verified myocardial fibrosis seems to be an indication for the initiation of amiodarone treatment(71).

Another application of CMR in CCC is its contribution at the prevention of stroke. As mentioned before, stroke can be the first manifestation of CCC(83,84).Left atrial enlargement, apical aneurysms and LV dysfunction prominent in CCC, predispose to the formation of intracavitary thrombi which frequently provoke cardioembolism and stroke (71,84). CMR has been proven superior than transesophageal and transthoracic echo in detecting intracavitary thrombi(132).Satisfyingly depicting apical aneurysms and thrombi with CMR and promptly starting anticoagulation ,clinicians can prevent cerebrovascular events in these patients.

CMR in differential diagnosis:

Delayed enhanced CMR actively contributes to the differential diagnosis of EMF and ChD from other cardiac conditions. Apical obliteration occurring in EMF can be misdiagnosed as apical HCM. Suboptimal apical echo views and inability to characterize tissue with echocardiography emphasize the complementary role of CMR in distinguishing between the two. Characteristically apical obliteration in EMF takes place during both phases of the cardiac cycle in sharp contrast with apical HCM where it occurs only in systole. Additionally, subendocardial enhancement pattern seen in EMF greatly differs from patchy midwall delayed enhancement observed in apical HCM(35,130).

Differentiation of cardiac amyloidosis from EMF in non-endemic countries can also be a peremptory challenge for clinicians as apical hypertrophy and restrictive filling pattern are present in both conditions. Abnormal gadolinium kinetics with early washout and unusually dark blood pool are findings suggestive of amyloid disease(137). Diffuse subendocardial or transmural delayed enhancement is observed in amyloidosis with transmurality being associated with ominous prognosis(114).

Of interest, CMR may facilitate the distinction between EMF and ChD especially in non-endemic countries. LV thrombi occupying the apex can be seen in the context of both the neglected cardiomyopathies(12,69).Aneurysmal apical myocardium with impaired contractility predisposes to thrombus formation in ChD(116,134) whereas in EMF systolic function of the apex is preserved and aneurysms are characteristically absent(138). Additionally, delayed enhancement pattern in ChD is inhomogeneous midwall, subepicardial, subendocardial or transmural with a predilection for the apical and inferolateral wall(67), diverging from that observed in EMF.

Cardiac sarcoidosis is also included in the differential diagnosis of the neglected cardiomyopathies. In patients with sarcoid, cine SSFP images demonstrate wall thinning and regional wall motion abnormalities with predilection for the septum and the lateral wall(116,130).

In early stages of the disease round foci with increased T2 and low T1 signal, surrounded by an area with increased T2 signal are highly suggestive of granulomas. In later stages, linear patchy delayed enhancement appears in regions where granulomas were located(137).

SWOT analysis:

Appraising our manuscript, this review is a scrutinizing study of the literature on the neglected cardiomyopathies. We thoroughly studied and presented current knowledge on the epidemiology etiology, natural course, clinical manifestations, treatment options and public health issues regarding both ChD and EMF. Moreover, existing diagnostic weapons against these conditions were analyzed focusing on the role of CMR. Its promising role on early diagnosis, prognosis, risk stratification, and response to treatment monitoring was demonstrated.

Nevertheless our work also has limitations. Firstly, articles recruitment for the review was a laborious procedure especially searching for articles about the role of CMR in EMF. Expectedly for two neglected clinical entities randomized clinical trials are lacking and some of the information included was based in case reports/series. Secondly, as it was outlined in our manuscript, the neglected cardiomyopathies are both correlated with poverty, afflicting low socioeconomic groups residing in rural stranded areas. CMR is a costly imaging modality, relatively inaccessible to these populations**.** Nonetheless the choice of connecting CMR, a cutting-edge imaging modality , with two forgotten cardiovascular diseases, was made deliberately. The reason was to showcase the necessity of unanimous accessibility of low socioeconomic groups in first-class health care facilities.

We hope that the application of CMR will illuminate the natural course of these clinical entities contributing to the development of novel and efficient treatments in the future.

Abbreviations	
EMF	Endomyocardial fibrosis
RVEMF	Right ventricular endomyocardial fibrosis
LVEMF	Left ventricular endomyocardial fibrosis
ChD	Chagas disease
CCC	Chronic chagasic cardiomyopathy
CMR	Cardiac magnetic resonance
LGE	Late gadolinium enhancement
DE	Delayed enhancement
MR	Mitral regurgitation
SSFP	Single Shot Free Precession
MV	Mitral valve
TV	Tricuspid valve
MR	Mitral Regurgitation
TR	Tricuspid regurgitation
LVEF	Left Ventricular Ejection Fraction
SCD	Sudden Cardiac Death
SNR	Signal to Noise Ratio
LVOT	Left ventricular Outflow Tract
LA/RA	Left Atrium/Right Atrium
LV/RV	Left ventricle/Right Ventricle
HCM	Hypertrophic cardiomyopathy
AF	Atrial Fibrilation
RHD	Rheumatic Heart Disease

References:

1. Zipes D,Libby P,Bonnow R,Mann DTomaselli G,Braunwald E. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Single Volume - 9780323462990 | US Elsevier Health Bookshop [Internet]. Eleventh Edition. Vol. 1. Elsevier; [cited 2020 Apr 23]. 1057 p. Available from: https://www.us.elsevierhealth.com/braunwalds-heart-disease-a-textbook-of-cardiovascular-medicine-single-volume-9780323462990.html

2. Groom ZC, Protopapas AD, Zochios V. Tropical diseases of the myocardium: a review. Int J Gen Med. 2017 Apr 7;10:101–11.

3. de Noya BA, Díaz-Bello Z, Colmenares C, Ruiz-Guevara R, Mauriello L, Muñoz-Calderón A, et al. Update on oral Chagas disease outbreaks in Venezuela: epidemiological, clinical and diagnostic approaches. Mem Inst Oswaldo Cruz. 2015 May;110(3):377–86.

4. Messenger LA, Miles MA, Bern C. Between a bug and a hard place: Trypanosoma cruzi genetic diversity and the clinical outcomes of Chagas disease. Expert Rev Anti Infect Ther. 2015 Aug 3;13(8):995–1029.

5. Coura JR, Viñas PA, Junqueira AC. Ecoepidemiology, short history and control of Chagas disease in the endemic countries and the new challenge for non-endemic countries. Mem Inst Oswaldo Cruz. 2014 Nov;109(7):856–62.

6. Chatelain E. Chagas disease research and development: Is there light at the end of the tunnel? Comput Struct Biotechnol J. 2017;15:98–103.

7. Rueda K, Trujillo JE, Carranza JC, Vallejo GA. Oral transmission of Trypanosoma cruzi: a new epidemiological scenario for Chagas' disease in Colombia and other South American countries. Biomédica. 2014 Dec 1;34(4):631–41.

8. Mocumbi AO, Stothard JR, Correia-de-Sá P, Yacoub M. Endomyocardial Fibrosis: an Update After 70 Years. Curr Cardiol Rep. 2019 Nov;21(11):148.

9. Denfield SW, Webber SA. Restrictive cardiomyopathy in childhood. Heart Fail Clin. 2010 Oct;6(4):445–52, viii.

10. Mocumbi AO. Endomyocardial fibrosis: A form of endemic restrictive cardiomyopathy. Glob Cardiol Sci Pract [Internet]. 2012 Jul 17 [cited 2020 Apr 9];2012(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239813/

11. Pérez-Molina JA, Molina I. Chagas disease. Lancet Lond Engl. 2018 06;391(10115):82–94.

12. Beaton A, Mocumbi AO. Diagnosis and Management of Endomyocardial Fibrosis. Cardiol Clin. 2017 Feb;35(1):87–98.

13. Lachaud M, Lachaud C, Sidi D, Menete A, Jouven X, Marijon E, et al. [Tropical endomyocardial fibrosis: Perspectives]. Ann Cardiol Angeiol (Paris). 2018 Apr;67(2):74–81.

14. Endomyocardial Fibrosis: an Update After 70 Years. - PubMed - NCBI [Internet]. [cited 2020 Apr 9]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31758352

15. Beck W. Cardiomyopathies in South Africa--a brief survey of the problem and current therapeutic approaches. Postgrad Med J. 1978 Jul;54(633):469–76.

16. Sliwa K, Damasceno A, Mayosi BM. Epidemiology and etiology of cardiomyopathy in Africa. Circulation. 2005 Dec 6;112(23):3577–83.

17. Bukhman G, Ziegler J, Parry E. Endomyocardial fibrosis: still a mystery after 60 years. PLoS Negl Trop Dis. 2008 Feb 27;2(2):e97.

18. Mocumbi AO. Endomyocardial fibrosis: A form of endemic restrictive cardiomyopathy. Glob Cardiol Sci Pract [Internet]. 2012 Jul 17 [cited 2020 Apr 9];2012(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239813/

19. Epidemiology of heart failure in sub-Saharan Africa. - PubMed - NCBI [Internet]. [cited 2020 Apr 11]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19210213

20. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. N Engl J Med. 2008 Jul 3;359(1):43–9.

21. Gupta PN, Kunju SM, Rajan B, Koshy AG, Vishwanathan S, George PS, et al. Geographical variation in the clinical presentation of endomyocardial fibrosis in India? Indian Heart J. 2018 Jan 1;70(1):56–65.

22. Sliwa K, Mocumbi AO. Forgotten cardiovascular diseases in Africa. Clin Res Cardiol Off J Ger Card Soc. 2010 Feb;99(2):65–74.

23. Huong DL, Wechsler B, Papo T, de Zuttere D, Bletry O, Hernigou A, et al. Endomyocardial fibrosis in Behçet's disease. Ann Rheum Dis. 1997 Mar;56(3):205–8.

24. Beaton A, Sable C, Brown J, Hoffman J, Mungoma M, Mondo C, et al. Genetic susceptibility to endomyocardial fibrosis. Glob Cardiol Sci Pract. 2014 Dec 31;2014(4):473–81.

25. Hypereosinophilic cardiac disease: Acta Cardiologica: Vol 72, No 1 [Internet]. [cited 2020 Apr 12]. Available from: https://www.tandfonline.com/doi/abs/10.1080/00015385.2017.1281546

26. Séguéla P-E, Iriart X, Acar P, Montaudon M, Roudaut R, Thambo J-B. Eosinophilic cardiac disease: Molecular, clinical and imaging aspects. Arch Cardiovasc Dis. 2015 Apr;108(4):258–68.

27. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome. Anatomic basis of mitral regurgitation and peripheral embolization. Circulation. 1983 Mar;67(3):572–8.

28. Spyrou N, Foale R. Restrictive cardiomyopathies: Curr Opin Cardiol. 1994 May;9(3):344–8.

29. Valiathan SM, Kartha CC. Endomyocardial fibrosis — the possible connexion with myocardial levels of magnesium and cerium. Int J Cardiol. 1990 Jul 1;28(1):1–5.

30. Valiathan MS. Endomyocardial fibrosis. Natl Med J India. 1993 Oct;6(5):212–6.

31. Grimaldi A, Mocumbi AO, Freers J, Lachaud M, Mirabel M, Ferreira B, et al. Tropical Endomyocardial Fibrosis: Natural History, Challenges, and Perspectives. Circulation. 2016 Jun 14;133(24):2503–15.

32. Bolarin DM, Andy JJ. Clinical feminization and serum testosterone levels in male patients with chronic African endomyocardial fibrosis. Trop Geogr Med. 1982;34(4):309–12.

33. Jaiyesimi F. Controversies and advances in endomyocardial fibrosis: a review. Afr J Med Med Sci. 1982 Jun;11(2):37–46.

34. Cherian G, Vijayaraghavan G, Krishnaswami S, Sukumar IP, John S, Jairaj PS, et al. Endomyocardial fibrosis: Report on the hemodynamic data in 29 patients and review of the results of surgery. Am Heart J. 1983 Apr 1;105(4):659–66.

35. de Carvalho FP, Azevedo CF. Comprehensive Assessment of Endomyocardial Fibrosis with Cardiac MRI: Morphology, Function, and Tissue Characterization. RadioGraphics. 2020 Jan 31;40(2):336–53.

36. Mocumbi AO. Right ventricular endomyocardial fibrosis (2013 Grover Conference series). Pulm Circ. 2014 Sep;4(3):363–9.

37. Endomyocardial fibrosis syndrome in Uganda - The Lancet [Internet]. [cited 2020 Apr 13]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)72932-9/fulltext

38. Hassan WM, Fawzy ME, Helaly SA, Hegazy H, Malik S. Pitfalls in Diagnosis and Clinical, Echocardiographic, and Hemodynamic Findings in Endomyocardial Fibrosis: A 25-Year Experience. CHEST. 2005 Dec 1;128(6):3985–92.

39. Somers K, Gunstone RF, Patel AK, D'Arbela PG. Atrial Arrhythmias in Endomyocardial Fibrosis. Cardiology. 1972;57(6):369–73.

40. Marangou J, Beaton A, Aliku TO, Nunes MCP, Kangaharan N, Reményi B. Echocardiography in Indigenous Populations and Resource Poor Settings. Heart Lung Circ. 2019 Sep 1;28(9):1427–35.

41. Nyshath Quader, Majesh Makan,Julio Perez. The Washington Manual of Echocardiography. 2nd Edition. Wolters Kluwer; 350 p.

42. Catherine Otto. Practice of Clinical Echocardiography - 9780323401258 | Elsevier Health Student and Practitioner Medical Books, ebooks and journals. 5th Edition. Elsevier; 1002 p.

43. Mahmoud A, Bansal M, Sengupta PP. New Cardiac Imaging Algorithms to Diagnose Constrictive Pericarditis Versus Restrictive Cardiomyopathy. Curr Cardiol Rep. 2017 May;19(5):43.

44. Mookadam F, Jiamsripong P, Raslan SF, Panse PM, Tajik AJ. Constrictive pericarditis and restrictive cardiomyopathy in the modern era. Future Cardiol. 2011 Jul;7(4):471–83.

45. Garcia MJ. Constrictive Pericarditis Versus Restrictive Cardiomyopathy? J Am Coll Cardiol. 2016 May 3;67(17):2061–76.

46. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008 Nov;67(11):1516–23.

47. Nabunnya YB, Kayima J, Longenecker CT, Josephson RA, Freers J. The safety and efficacy of prednisolone in preventing reaccumulation of ascites among endomyocardial fibrosis patients in Uganda: a randomized clinical trial. BMC Res Notes [Internet]. 2015 Dec 15 [cited 2020 Apr 21];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4678569/

48. Ferrario Carlos M., Schiffrin Ernesto L. Role of Mineralocorticoid Receptor Antagonists in Cardiovascular Disease. Circ Res. 2015 Jan 2;116(1):206–13.

49. Mocumbi AOH, Falase AO. Recent advances in the epidemiology, diagnosis and treatment of endomyocardial fibrosis in Africa. Heart. 2013 Oct 15;99(20):1481–7.

50. Schneider U, Jenni R, Turina J, Turina M, Hess OM. Long-term follow up of patients with endomyocardial fibrosis: effects of surgery. Heart Br Card Soc. 1998 Apr;79(4):362–7.

51. Mocumbi AO, Carrilho C, Burke MM, Wright G, Yacoub MH. Emergency surgical treatment of advanced endomyocardial fibrosis in Mozambique. Nat Rev Cardiol. 2009 Mar;6(3):210–4.

52. Early surgical results in the treatment of endomyocardial fibrosis. A Brazilian cooperative study. Eur J Cardiothorac Surg. 1989 Sep 1;3(5):408–13.

53. Benziger CP, do Carmo GAL, Ribeiro ALP. Chagas Cardiomyopathy: Clinical Presentation and Management in the Americas. Cardiol Clin. 2017 Feb;35(1):31–47.

54. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MOC. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol. 2012 Oct;9(10):576–89.

55. Tanowitz HB, Machado FS, Spray DC, Friedman JM, Weiss OS, Lora JN, et al. Developments in the management of Chagas cardiomyopathy. Expert Rev Cardiovasc Ther. 2015 Dec;13(12):1393–409.

56. Bonney KM. Chagas disease in the 21st Century: a public health success or an emerging threat? Parasite [Internet]. 2014 [cited 2020 Apr 17];21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3952655/

57. Barbosa M das GV, Ferreira JMBB, Arcanjo ARL, Santana RAG, Magalhães LKC, Magalhães LKC, et al. Chagas disease in the State of Amazonas: history, epidemiological evolution, risks of endemicity and future perspectives. Rev Soc Bras Med Trop. 2015 Jun;48(suppl 1):27–33.

58. Carlier Y, Sosa-Estani S, Luquetti AO, Buekens P. Congenital Chagas disease: an update. Mem Inst Oswaldo Cruz. 2015 May;110(3):363–8.

59. Requena-Méndez A, Aldasoro E, Lazzari E de, Sicuri E, Brown M, Moore DAJ, et al. Prevalence of Chagas Disease in Latin-American Migrants Living in Europe: A Systematic Review and Meta-analysis. PLoS Negl Trop Dis. 2015;9(2):e0003540.

60. Strasen J, Williams T, Ertl G, Zoller T, Stich A, Ritter O. Epidemiology of Chagas disease in Europe: many calculations, little knowledge. Clin Res Cardiol Off J Ger Card Soc. 2014 Jan;103(1):1–10.

61. Malik LH, Singh GD, Amsterdam EA. The Epidemiology, Clinical Manifestations, and Management of Chagas Heart Disease. Clin Cardiol. 2015 May 21;38(9):565–9.

62. Healy C, Viles-Gonzalez JF, Sáenz LC, Soto M, Ramírez JD, d'Avila A. Arrhythmias in chagasic cardiomyopathy. Card Electrophysiol Clin. 2015 Jun;7(2):251–68.

63. Martí-Carvajal AJ, Kwong JSW. Pharmacological interventions for treating heart failure in patients with Chagas cardiomyopathy. Cochrane Database Syst Rev. 2016 Jul 8;7:CD009077.

64. Pereira C de B, Markman B. Clinical and Echocardiographic Predictors of Mortality in Chagasic Cardiomyopathy - Systematic Review. Arq Bras Cardiol. 2014 Jun;102(6):602–10.

65. Acosta IC, Pérez-Tanoira R, Prieto-Pérez L, Úbeda AC, Álvarez Álvarez B, Antoranz PA, et al. Chagas' heart disease: Descriptive analysis of 141 patients in a hospital of Madrid, Spain. Travel Med Infect Dis. 2020 Apr 22;101690.

66. Sabino EC, Ribeiro AL, Salemi VMC, Di Lorenzo Oliveira C, Antunes AP, Menezes MM, et al. Ten-Year Incidence of Chagas Cardiomyopathy Among Asymptomatic Trypanosoma cruzi–Seropositive Former Blood Donors. Circulation. 2013 Mar 12;127(10):1105–15.

67. Belisario Falchetto E, Costa SCS, Rochitte CE. Diagnostic Challenges of Chagas Cardiomyopathy and CMR Imaging. Glob Heart. 2015 Sep 1;10(3):181.

68. Andrade JP, Marin-Neto JA, Paola A a. V, Vilas-Boas F, Oliveira GMM, Bacal F, et al. I Latin American Guideline for the Diagnosis and Treatment of Chagas' Heart Disease. Arq Bras Cardiol. 2011;97(2):01–48.

69. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MOC. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol. 2012 Oct;9(10):576–89.

70. Ministério da Saúde. Secretaria de Vigilância em Saúde. [Brazilian Consensus on Chagas disease]. Rev Soc Bras Med Trop. 2005;38 Suppl 3:7–29.

71. Nunes MCP, Beaton A, Acquatella H, Bern C, Bolger AF, Echeverría LE, et al. Chagas Cardiomyopathy: An Update of Current Clinical Knowledge and Management: A Scientific Statement From the

American Heart Association. Circulation [Internet]. 2018 Sep 18 [cited 2020 Apr 21];138(12). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000599

72. De Ponti R, Marazzato J, Bagliani G, Leonelli FM, Padeletti L. Sick Sinus Syndrome. Card Electrophysiol Clin. 2018 Jun;10(2):183–95.

73. Brito BO de F, Ribeiro ALP, Brito BO de F, Ribeiro ALP. Electrocardiogram in Chagas disease. Rev Soc Bras Med Trop. 2018 Oct;51(5):570–7.

74. Lima-Costa MF, Matos DL, Ribeiro ALP. Chagas disease predicts 10-year stroke mortality in community-dwelling elderly: the Bambui cohort study of aging. Stroke. 2010 Nov;41(11):2477–82.

75. Ribeiro ALP, Marcolino MS, Prineas RJ, Lima-Costa MF. Electrocardiographic Abnormalities in Elderly Chagas Disease Patients: 10-Year Follow-Up of the Bambuí Cohort Study of Aging. J Am Heart Assoc Cardiovasc Cerebrovasc Dis [Internet]. 2014 Feb 28 [cited 2020 Apr 23];3(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959704/

76. Navarro M, Navaza B, Guionnet A, López-Vélez R. Chagas Disease in Spain: Need for Further Public Health Measures. PLoS Negl Trop Dis. 2012;6(12):e1962.

77. Cardoso R, Garcia D, Fernandes G, He LI, Lichtenberger P, Viles-Gonzalez J, et al. The Prevalence of Atrial Fibrillation and Conduction Abnormalities in Chagas' Disease: A Meta-Analysis. J Cardiovasc Electrophysiol. 2016 Feb;27(2):161–9.

78. Pereira C de B, Markman B. Clinical and Echocardiographic Predictors of Mortality in Chagasic Cardiomyopathy - Systematic Review. Arq Bras Cardiol. 2014 Jun;102(6):602–10.

79. Barbosa MPT, Carmo AAL do, Rocha MO da C, Ribeiro ALP. Ventricular arrhythmias in Chagas disease. Rev Soc Bras Med Trop. 2015 Feb;48(1):4–10.

80. Healy C, Viles-Gonzalez JF, Sáenz LC, Soto M, Ramírez JD, d'Avila A. Arrhythmias in chagasic cardiomyopathy. Card Electrophysiol Clin. 2015 Jun;7(2):251–68.

81. Barros ML, Ribeiro A, Nunes M do C, Rocha MO da C. [Association between left ventricular wall motion abnormalities and ventricular arrhythmia in the indeterminate form of Chagas disease]. Rev Soc Bras Med Trop. 2011 Apr;44(2):213–6.

82. Tanowitz HB, Machado FS, Spray DC, Friedman JM, Weiss OS, Lora JN, et al. Developments in the management of Chagas cardiomyopathy. Expert Rev Cardiovasc Ther. 2015 Dec;13(12):1393–409.

83. Carod-Artal FJ, Vargas AP, Horan TA, Nunes LGN. Chagasic Cardiomyopathy Is Independently Associated With Ischemic Stroke in Chagas Disease. Stroke. 2005 May 1;36(5):965–70.

84. Cardoso RN, Macedo FYB, Garcia MN, Garcia DC, Benjo AM, Aguilar D, et al. Chagas Cardiomyopathy is Associated With Higher Incidence of Stroke: A Meta-analysis of Observational Studies. J Card Fail. 2014 Dec 1;20(12):931–8.

85. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. Chagas cardiomyopathy is associated with higher incidence of stroke: a meta-analysis of observational studies [Internet]. Centre for Reviews and Dissemination (UK); 2014 [cited 2017 Apr 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK291191/

86. Rassi AJr, Rassi A, Little WC, Xavier SS, Rassi SG, Rassi AG, et al. Development and Validation of a Risk Score for Predicting Death in Chagas' Heart Disease. N Engl J Med. 2006 Aug 24;355(8):799–808.

87. Castillo-Riquelme M. Chagas disease in non-endemic countries. Lancet Glob Health. 2017 Apr 1;5(4):e379–80.

88. Dias JCP. Evolution of Chagas disease screening programs and control programs: historical perspective. Glob Heart. 2015 Sep;10(3):193–202.

89. Traina M, Meymandi S, Bradfield JS. Heart Failure Secondary to Chagas Disease: an Emerging Problem in Non-endemic Areas. Curr Heart Fail Rep. 2016 Dec;13(6):295–301.

90. Chatelain E. Chagas disease research and development: Is there light at the end of the tunnel? Comput Struct Biotechnol J. 2016 Dec 14;15:98–103.

91. Bonney KM. Chagas disease in the 21st Century: a public health success or an emerging threat? Parasite [Internet]. 2014 [cited 2017 Apr 5];21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3952655/

92. Vannucchi V, Tomberli B, Zammarchi L, Fornaro A, Castelli G, Pieralli F, et al. Chagas disease as a cause of heart failure and ventricular arrhythmias in patients long removed from endemic areas: an emerging problem in Europe. J Cardiovasc Med Hagerstown Md. 2015 Dec;16(12):817–23.

93. Acquatella H, Asch FM, Barbosa MM, Barros M, Bern C, Cavalcante JL, et al. Recommendations for Multimodality Cardiac Imaging in Patients with Chagas Disease: A Report from the American Society of Echocardiography in Collaboration With the InterAmerican Association of Echocardiography

(ECOSIAC) and the Cardiovascular Imaging Department of the Brazilian Society of Cardiology (DIC-SBC). J Am Soc Echocardiogr. 2018 Jan 1;31(1):3–25.

94. Garcia-Alvarez A, Sitges M, Pinazo M-J, Regueiro-Cueva A, Posada E, Poyatos S, et al. Chagas Cardiomiopathy: The Potential of Diastolic Dysfunction and Brain Natriuretic Peptide in the Early Identification of Cardiac Damage. PLoS Negl Trop Dis [Internet]. 2010 Sep 21 [cited 2020 Apr 25];4(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2943653/

95. Nunes M do CP, Beloti FR, Lima MMO, Barbosa MM, Pinto Filho MM, de Barros MVL, et al. Functional capacity and right ventricular function in patients with Chagas heart disease. Eur J Echocardiogr J Work Group Echocardiogr Eur Soc Cardiol. 2010 Aug;11(7):590–5.

96. Muratore CA, Baranchuk A. Current and emerging therapeutic options for the treatment of chronic chagasic cardiomyopathy. Vasc Health Risk Manag. 2010;6:593–601.

97. Issa VS, Amaral AF, Cruz FD, Ferreira SMA, Guimarães GV, Chizzola PR, et al. β-Blocker Therapy and Mortality of Patients With Chagas CardiomyopathyCLINICAL PERSPECTIVE. Circ Heart Fail. 2010 Jan 1;3(1):82–8.

98. Botoni FA, Poole-Wilson PA, Ribeiro ALP, Okonko DO, Oliveira BMR, Pinto AS, et al. A randomized trial of carvedilol after renin-angiotensin system inhibition in chronic Chagas cardiomyopathy. Am Heart J. 2007 Apr 1;153(4):544.e1-544.e8.

99. Oliveira-Filho J. Stroke and brain atrophy in chronic Chagas disease patients: A new theory proposition. Dement Neuropsychol. 2009;3(1):22–6.

100. Fiorelli AI, Santos RHB, Oliveira JL, Lourenço-Filho DD, Dias RR, Oliveira AS, et al. Heart Transplantation in 107 Cases of Chagas' Disease. Transplant Proc. 2011 Jan 1;43(1):220–4.

101. Campos de Carvalho AC, Bastos Carvalho A. Stem Cell-Based Therapies in Chagasic Cardiomyopathy. BioMed Res Int [Internet]. 2015 [cited 2017 Apr 7];2015. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4486210/

102. Malik LH, Singh GD, Amsterdam EA. The Epidemiology, Clinical Manifestations, and Management of Chagas Heart Disease. Clin Cardiol. 2015 Sep;38(9):565–9.

103. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. Eur Heart J. 2009 May 1;30(10):1245–53.

104. Cardinalli-neto A, Bestetti RB, Cordeiro JA. To the Editor: J Cardiovasc Electrophysiol. 2008 Apr 1;19(4):E34–5.

105. Martinelli M, Rassi A, Marin-Neto JA, de Paola AAV, Berwanger O, Scanavacca MI, et al. CHronic use of Amiodarone aGAinSt Implantable cardioverter-defibrillator therapy for primary prevention of death in patients with Chagas cardiomyopathy Study: rationale and design of a randomized clinical trial. Am Heart J. 2013 Dec;166(6):976-982.e4.

106. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, et al. EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias. Heart Rhythm. 2009 Jun;6(6):886–933.

107. Marin-Neto JA, Cunha-Neto E, Maciel BC, Simões MV. Pathogenesis of chronic Chagas heart disease. Circulation. 2007 Mar 6;115(9):1109–23.

108. Fabbro DL, Danesi E, Olivera V, Codebó MO, Denner S, Heredia C, et al. Trypanocide Treatment of Women Infected with Trypanosoma cruzi and Its Effect on Preventing Congenital Chagas. PLoS Negl Trop Dis [Internet]. 2014 Nov 20 [cited 2020 Apr 23];8(11). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4239005/

109. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi AJr, Rosas F, et al. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. N Engl J Med. 2015 Oct 1;373(14):1295–306.

110. Strasen J, Williams T, Ertl G, Zoller T, Stich A, Ritter O. Epidemiology of Chagas disease in Europe: many calculations, little knowledge. Clin Res Cardiol Off J Ger Card Soc. 2014 Jan;103(1):1–10.

111. Soriano-Arandes A, Angheben A, Serre-Delcor N, Treviño-Maruri B, Gómez I Prat J, Jackson Y. Control and management of congenital Chagas disease in Europe and other non-endemic countries: current policies and practices. Trop Med Int Health TM IH. 2016 May;21(5):590–6.

112. Requena-Méndez A, Bussion S, Aldasoro E, Jackson Y, Angheben A, Moore D, et al. Cost-effectiveness of Chagas disease screening in Latin American migrants at primary health-care centres in Europe: a Markov model analysis. Lancet Glob Health. 2017 Apr;5(4):e439–47.

113. Saeed M, Liu H, Liang C-H, Wilson MW. Magnetic resonance imaging for characterizing myocardial diseases. Int J Cardiovasc Imaging. 2017 Sep 1;33(9):1395–414.

114. Patel AR, Kramer CM. Role of Cardiac Magnetic Resonance in the Diagnosis and Prognosis of Non-Ischemic Cardiomyopathy. JACC Cardiovasc Imaging. 2017 Oct;10(10 Pt A):1180–93.

115. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance, et al. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson. 2013 Oct 8;15(1):91.

116. Salemi VMC, Rochitte CE, Shiozaki AA, Andrade JM, Parga JR, de Ávila LF, et al. Late Gadolinium Enhancement Magnetic Resonance Imaging in the Diagnosis and Prognosis of Endomyocardial Fibrosis Patients. Circ Cardiovasc Imaging. 2011 May;4(3):304–11.

117. Oorschot JWM van, Gho JMIH, Hout GPJ van, Froeling M, Lorkeers SJJ of, Hoefer IE, et al. Endogenous contrast MRI of cardiac fibrosis: Beyond late gadolinium enhancement. J Magn Reson Imaging. 2015;41(5):1181–9.

118. Hunold P, Schlosser T, Vogt FM, Eggebrecht H, Schmermund A, Bruder O, et al. Myocardial Late Enhancement in Contrast-Enhanced Cardiac MRI: Distinction Between Infarction Scar and Non–Infarction-Related Disease. Am J Roentgenol. 2005 May;184(5):1420–6.

119. Ramalho M, Ramalho J, Burke LM, Semelka RC. Gadolinium Retention and Toxicity-An Update. Adv Chronic Kidney Dis. 2017;24(3):138–46.

120. Kramer CM, Chandrashekhar Y, Narula J. The Tissue Issue: T1 Mapping and the Myocardium. JACC Cardiovasc Imaging. 2016 Jan 1;9(1):88–90.

121. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 Mapping: Basic Techniques and Clinical Applications. JACC Cardiovasc Imaging. 2016 Jan 1;9(1):67–81.

122. Kim PK, Hong YJ, Im DJ, Suh YJ, Park CH, Kim JY, et al. Myocardial T1 and T2 Mapping: Techniques and Clinical Applications. Korean J Radiol. 2017;18(1):113–31.

123. Kammerlander AA, Marzluf BA, Zotter-Tufaro C, Aschauer S, Duca F, Bachmann A, et al. T1 Mapping by CMR Imaging: From Histological Validation to Clinical Implication. JACC Cardiovasc Imaging. 2016 Jan 1;9(1):14–23.

124. Thavendiranathan P, Walls M, Giri S, Verhaert D, Rajagopalan S, Moore S, et al. Improved detection of myocardial involvement in acute inflammatory cardiomyopathies using T2 mapping. Circ Cardiovasc Imaging. 2012 Jan;5(1):102–10.

125. Cury Ricardo C., Abbara Suhny, Sandoval Larry J-Diaz, Houser Stuart, Brady Thomas J., Palacios Igor F. Visualization of Endomyocardial Fibrosis by Delayed-Enhancement Magnetic Resonance Imaging. Circulation. 2005 Mar 8;111(9):e115–7.

126. Qureshi N, Amin F, Chatterjee D, Prasad S, Al-Obaidi M, Missouris C. MR imaging of endomyocardial fibrosis (EMF). Int J Cardiol. 2011 May 19;149(1):e36–7.

127. Paydar A, Ordovas KG, Reddy GP. Magnetic Resonance Imaging for Endomyocardial Fibrosis. Pediatr Cardiol. 2008 Sep;29(5):1004–5.

128. Syed IS, Martinez MW, Feng D-L, Glockner JF. Cardiac magnetic resonance imaging of eosinophilic endomyocardial disease. Int J Cardiol. 2008 Jun;126(3):e50–2.

129. Carneiro AC, Mochiduky RI, Zancaner LF, Cabeda EV, Moreira VM, Ribeiro MS, et al. A new typical finding in late gadolinium enhanced images for the diagnosis of endomyocardial fibrosis - the double V sign. J Cardiovasc Magn Reson. 2011 Feb 2;13(Suppl 1):O40.

130. Dato I. How to recognize endomyocardial fibrosis?: J Cardiovasc Med. 2015 Aug;16(8):547–51.

131. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, et al. Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy. Circulation [Internet]. 2010 Aug 31 [cited 2020 May 6]; Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.109.924167

132. Srichai MB, Junor C, Rodriguez LL, Stillman AE, Grimm RA, Lieber ML, et al. Clinical, imaging, and pathological characteristics of left ventricular thrombus: a comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. Am Heart J. 2006 Jul;152(1):75–84.

133. Shapiro S, Pinney SP, Anyanwu AC, Garcia MJ. An atypical presentation of endomyocardial fibrosis diagnosed by cardiac MRI. Circ Heart Fail. 2009 Jan;2(1):77–80.

134. Regueiro A, García-Álvarez A, Sitges M, Ortiz-Pérez JT, De Caralt MT, Pinazo MJ, et al. Myocardial involvement in Chagas disease: insights from cardiac magnetic resonance. Int J Cardiol. 2013 Apr 30;165(1):107–12.

135. Sarabanda AVL, Sosa E, Simões MV, Figueiredo GL, Pintya AO, Marin-Neto JA. Ventricular tachycardia in Chagas' disease: a comparison of clinical, angiographic, electrophysiologic and myocardial perfusion disturbances between patients presenting with either sustained or nonsustained forms. Int J Cardiol. 2005 Jun 22;102(1):9–19.

136. Uellendahl M, Siqueira MEM de, Calado EB, Kalil-Filho R, Sobral D, Ribeiro C, et al. Cardiac Magnetic Resonance-Verified Myocardial Fibrosis in Chagas Disease: Clinical Correlates and Risk Stratification. Arq Bras Cardiol. 2016 Nov;107(5):460–6.

137. Gupta A, Singh Gulati G, Seth S, Sharma S. Cardiac MRI in restrictive cardiomyopathy. Clin Radiol. 2012 Feb;67(2):95–105.

138. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J. 2005 Aug 1;26(15):1461–74.