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Computational Identification of Ventricular Arrhythmia Risk in Pediatric Myocarditis

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Abstract

Introduction: Children with myocarditis have increased risk of ventricular tachycardia (VT) due to myocardial inflammation and remodeling. There is currently no accepted method for VT risk stratification in this population. We hypothesized that personalized models developed from cardiac late gadolinium enhancement magnetic resonance imaging (LGE-MRI) could determine VT risk in patients with myocarditis using a previously-validated protocol.

Methods: Personalized three-dimensional computational cardiac models were reconstructed from LGE-MRI scans of 12 patients diagnosed with myocarditis. Four patients with clinical VT and eight patients without VT were included in this retrospective analysis. In each model, we incorporated a personalized spatial distribution of fibrosis and myocardial fiber orientations. Then, VT inducibility was assessed in each model by pacing rapidly from 26 sites distributed throughout both ventricles.

Results: Sustained reentrant VT was induced from multiple pacing sites in all patients with clinical VT. In the eight patients without clinical VT, we were unable to induce sustained reentry in our simulations using rapid ventricular pacing.

Conclusion: Application of our non-invasive approach in children with myocarditis has the potential to correctly identify those at risk for developing VT.

Keywords

myocarditis; arrhythmia; MRI; computational; electrophysiology

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Introduction

Myocarditis is a relatively common cause of morbidity and mortality in the young, especially in cases of infectious etiology. The true incidence of myocarditis is likely underestimated due to both diagnostic uncertainty and the wide spectrum of presentation ranging from sudden death to mild illness with complete recovery [1–8].

Based on evidence gathered across multiple cohorts on post-mortem exam, histopathologic evidence of myocarditis has been identified in up to 20% of young adults presenting with sudden death [8–11]. The morbidity and mortality in myocarditis are related to the development of dilated cardiomyopathy and ventricular tachycardia (VT), reported in up to 11.5% of patients in the acute setting and 5.4% of patients in a recent long term follow up study [3–7,12–13]. The infection itself as well as the subsequent host response cause myocardial electromechanical remodeling and ion channel level changes [14–23]. These changes, like those seen in various forms of non-infectious cardiomyopathy, play a role in the increased arrhythmogenicity seen in patients with myocarditis [15,19,22–24].

Cardiac MRI has evolved as a useful diagnostic tool in the evaluation of suspected myocarditis as endomyocardial biopsy has been increasingly avoided [25–30]. Despite the increased role of MRI, a clear connection has yet to be made between specific findings on MRI, disease course, and outcomes [31–35]. Myocardial inflammation and fibrosis are visualized on cardiac MRI using late gadolinium enhancement (LGE) sequences [32]. Nonetheless, the specific association of LGE with adverse outcomes in myocarditis remains undefined [25–28,30–34]. Previous studies have confirmed though that the development of VT in myocarditis is associated with worse outcomes and increased resource utilization [36–38].

Outside of computational fluid dynamic studies and basic three-dimensional printing applications, the use of organ-scale computational simulations in pediatric cardiology has been quite limited [39–41]. In patients with ischemic cardiomyopathy, personalized three-dimensional computer models based on late gadolinium enhanced MRI (LGE-MRI) scans have been used to successfully determine an individual's likelihood for developing VT [42–44]. In this retrospective study, we determined whether this novel MRI-based computational approach could be similarly utilized in pediatric patients with myocarditis to noninvasively predict risk of VT.

Materials and methods

This institutional review board approved retrospective pilot study included 12 patients under 19 years of age diagnosed with myocarditis. Patients were identified by querying our echocardiographic database, which includes data beginning in 2014, for the diagnosis of myocarditis. Chart review identified patients who had appropriate LGE-MRI sequences and were diagnosed with myocarditis. The diagnosis of myocarditis was based on clinical parameters including elevated serum troponin, history of recent or current viral illness, abnormalities on cardiac imaging including echocardiography and MRI, and endomyocardial biopsy in all cases of ventricular assist device implantation or cardiac

transplantation. Cardiac MRI was performed for each patient while admitted to our center during their initial presentation and diagnosis. Patients with acute and chronic myocarditis were included. Patients with acute myocarditis have evidence of myocardial damage hallmarked by elevated troponin, acute symptoms such as chest pain, and active or recent febrile illness. Patients with chronic myocarditis, a disease of myocardial fibrosis and structural remodeling, presented with symptoms and findings of dilated cardiomyopathy with a history of a febrile illness or prior diagnosis of acute myocarditis. Patients were considered VT positive if there was telemetric evidence of multiple episodes of non-sustained VT or any episode of sustained VT during their initial hospitalization. Any VT less than 30 seconds was considered non-sustained with VT defined as at least three consecutive wide complex beats at a rate greater than 120 beats per minute. All patients were on continuous telemetric monitoring while admitted to our institution during their initial presentation and MRI acquisition. Chart review identified 18 patients, with 12 ultimately included in the study. Three patients were excluded from the study as they had a later-identified genetic mutation associated with automatic or triggered VT. Another three patients were excluded because their MRI-LGE sequence was so affected by imaging artifact (e.g. phase aliasing, motion artifact) as to be unusable in our model reconstruction pipeline.

As part of their diagnostic evaluation, all patients underwent standard clinical contrast-enhanced short-axis MRI (Siemens 1.5 T, Aera or Avanto). Each gated, diastolic geometry short axis stack consisted of 10-15 contiguous slices with an 8-10 mm slice thickness. LGE images were acquired 15-20 minutes after a total injection of 0.1 mmol/kg of contrast agent (Magnevist or Gadavist, Bayer AG, Germany) with an inversion recovery fast gradient-echo pulse sequence. Imaging parameters were as follows: repetition time 4.2-9.8 ms, echo time 1.04-1.14 ms, average in-plane spatial resolution 1.9 mm, and inversion time adjusted to null the signal of normal myocardium (255-360 ms). All imaging acquisition parameters were standard for our institution [42,45].

The short axis LGE stacks were segmented in blinded fashion using our previously published segmentation and interpolation method [43,46,47]. Briefly, seed points were placed on each magnitude-corrected short axis slice using CardioViz3D (INRIA, Sophia-Antipolis, France) to generate the epicardial and endocardial boundaries for the right and left ventricles. The left ventricular myocardium was then segmented into three tissue types: healthy tissue, grey zone, and scar using Matlab (MathWorks Inc, Natick, United States). This was accomplished using our previously described grey-level thresholding method where in autonomous fashion the mean and standard deviation of the voxel intensities of the myocardium were calculated [48]. The grey-level value corresponding to +3 standard deviation was assigned as the upper limit for normal tissue while the value corresponding to +5 was assigned as the upper limit for grey zone.

The right ventricular myocardium was modeled as healthy tissue due to the inherent difficulty segmenting the thin right ventricular myocardium without erroneously including blood pool or artifact as enhanced myocardium.

Using the segmented geometry created from each short axis stack, tetrahedral meshes were developed as described previously [49]. This step critically preserves the geometric details of both ventricles and the boundaries between different tissue regions. Patient specific myocardial fiber orientations were then assigned for each heart model using a methodology previously developed by our team [50].

Electrophysiological properties in our cardiac models were implemented as described in our previously published papers [43,43]. We chose to use the same properties from prior work on ischemic cardiomyopathy because of the similarities in the cellular and tissue level pathology responsible for arrhythmogenesis in both myocarditis and ischemic cardiomyopathy [14–23]. Briefly, regions of scar were modeled as non-conductive while human ventricular cell action potential properties were assigned to both grey zone and healthy tissue but with different cell-scale properties [51]. This resulted in an altered action potential morphology in the grey zone, as compared to tissue remote from tissue modeled as scar, with longer action potential duration, slurred upstroke, and decreased peak amplitude (Figure 1). Tissue level conductivities were adjusted based on tissue type [42,43]. To account for the known connexin-43 remodeling near areas of scar or fibrosis, transverse grey zone conductivity was decreased by 90% from healthy tissue [42,43].

Computational, non-invasive electrophysiology studies were then performed on a high-power computing cluster using the software package CARP (Cardiosolv, LLC) to determine propensity of each heart model to develop ventricular arrhythmia [42,43,52–54]. Each model was paced from 26 pacing locations, based on American Heart Association segments, distributed throughout both ventricles [55]. In the same fashion as previously validated, all models were paced endocardially from each of the 26 locations for 6 beats (S1), at a cycle length of 600ms, followed by a premature stimulus (S2), initially given at 90% of S1 cycle length [42]. The timing between S1 and S2 was shortened in 10 ms increments until VT was induced. If VT was not induced, a second premature stimulus (S3) was delivered after S2. If VT was not induced either, a third premature stimulus (S4) was delivered after S3. Sustained VT in the computational electrophysiology studies was defined as three seconds of self-perpetuating activity following delivery of the final stimulus [42,44,54].

Descriptive statistics were calculated for all variables of interest and included count, median, mean, and standard deviation when appropriate. The independent samples t-test or chi-square test were used to compare differences between patients with and without clinical VT (considered statistically significant when p value ≤ 0.05).

Results

Our protocol, with blinded model generation and execution of all simulations, correctly identified arrhythmia propensity in all patients. Upon completion of our patient specific analysis, VT was induced in models that corresponded to patients in whom clinical VT was documented. Furthermore, we were unable to induce VT in models from patients without documented clinical VT.

All our patients were teenagers (median age 15 years) and our cohort was 70% male (Table 1). Four VT positive patients were included (Table 1). Following recognition of VT, patient 4 required only observation, patient 12 required changes to medical management and eventually underwent ventricular assist device (VAD) implantation, and patients 1 and 11 had more urgent VAD implantation following their VT. There was not a significant difference in ejection fraction or peak troponin between patients with and without VT (Table 2). There was though a significant difference between these groups in terms of indexed end diastolic volume and end systolic volume. The presence of clinical VT in our cohort was associated with eventual transplantation ($p=.030383$) but not phase of disease ($p=.583882$). Mean ejection fraction was markedly lower in patients who proceeded to transplant or VAD implantation compared to patients who recovered (15% vs 56.5%, $p<.0001$).

The ventricular geometry and geometric tissue type patterns were unique for each patient's heart model (Figure 2). The proportion of healthy tissue ($79.5\pm3.6\%$), grey-zone ($16.6\pm2.8\%$), and dense fibrosis or scar ($3.9\pm1.2\%$) was similar in all patients (Table 2). There was no statistically significant association between the proportion of any of the tissue types, clinical VT status, or VT inducibility in our models.

Following our rapid ventricular pacing protocol, we were able to induce sustained reentrant VT in the models of the four patients with clinical VT. The models for these four patients were all inducible at S4 in our pacing protocol. Patient 1 was inducible from endocardial pacing sites in each ventricle. Patient 4 was inducible from a right ventricular pacing site while patients 11 and 12 were inducible from left ventricular pacing sites. Upon review of activation maps from our simulation results, the organizing centers of reentry were located in regions of fibrosis in our high-resolution models (Figure 3). The activation maps for these patients demonstrate unique patterns of reentry with areas of fibrotic tissue serving as either an anchor point for rotor formation or for figure-of-eight type reentry (Figure 3, Online Resources 1 and 2). In patients one and twelve, the reentry occurs in figure-of-eight fashion where there is an isthmus of healthy tissue between two regions of scar within the left ventricular myocardium. On the other hand, the simulated reentry in patients four and eleven is in the pattern of a circular, reentrant rotor.

Discussion

This study demonstrates the potential for our non-invasive, MRI-based computational methodology to correctly identify arrhythmogenic propensity in pediatric patients with myocarditis. In all computational models reconstructed from MRI scans of patients who experienced clinical VT, our simulations of programmed endocardial pacing resulted in the initiation of sustained reentrant arrhythmia. In contrast, when the same pacing protocol was applied in models corresponding to VT-negative patients in our study, we were not able to observe a single instance of simulated reentry.

Our study included patients in the acute phase and chronic phase of myocarditis. In the acute phase, inflammation itself creates arrhythmogenic foci throughout the myocardium. Increased extracellular space from tissue edema decreases local myocardial conduction velocity in regions which can then anchor reentry [15,19,22]. Abnormal calcium cycling and

downregulation of potassium channels prolong action potential duration while altered expression of gap junction proteins and disruption of dystrophin also contribute to an increased substrate for VT [14,16–18,20]. In the chronic phase, longstanding myocardial inflammation can occur even after functional myocardial recovery [13,15]. In the setting of chronic myocyte injury, a persistent substrate for reentrant circuit formation develops in the form of replacement type fibrosis leading to scar formation [20–22]. Similar to the acute phase, the host immune response in the chronic phase of disease results in abnormal ion channel behavior and a prolonged action potential duration [13–23]. Our modeling pipeline included regional variability of both action potential duration and conductivity to account for these known arrhythmogenic changes in myocarditis.

Regions of increased intensity on LGE-MRI may represent some combination of fibrosis and edema [25,27]. Because our pipeline depends on signal intensity of the LGE-MRI sequence to identify tissue types and thus regions with different electrophysiologic properties in our models, our process may be falsely identifying edema as fibrosis in patients with acute myocarditis. However, regions of increased interstitial edema do act as anchors for reentry due to altered conduction velocity and myocyte decoupling in areas of inflammation [15,19,22]. So, even though our method may classify actual areas of edema as scar or grey zone in patients with acute myocarditis, it still correctly accounts for the appropriate electrical remodeling within these regions by utilizing altered action potential behavior and tissue specific conduction velocity. In chronic myocarditis, where enhanced tissue on LGE-MRI source images is more likely replacement type fibrosis, our pipeline correctly models enhanced tissue as scar with surrounding grey zone.

Triggered or automatic VT can occur in myocarditis [13,15]. The cytokine response which causes electromechanical remodeling of the myocardium is present both with and without active inflammation [20–23]. Triggered VT is more common in the acute setting because of greater derangement of the action potential duration, ion channel and gap junction behavior, and effective refractory period [14–20]. Though our methodology, designed to only evaluate the arrhythmogenic propensity of the remodeled substrate, does not account for triggered VT, our models do account for the factors responsible for increased reentrant VT in the acute setting of myocarditis.

Regardless of disease state, our methodology critically also incorporates the patient specific spatial distribution of areas of enhancement and thus represents the complex interplay of different tissue geometries and activation patterns of the myocardium [44,56]. The finding that in our models the relative amount of healthy tissue, grey zone, and scar were quite similar highlights the role of the geometric distribution of scar and grey-zone in the development of arrhythmia. The spatial relationship of areas of scar and healthy tissue is known to play a role in rotor generation and in anchoring reentrant wavefronts in myocarditis [13,15,19,22,54,56]. Our high-resolution organ scale computational models, based on patient specific clinical MRI data, demonstrate the connection between arrhythmia substrate and propensity for VT.

In our study, there were several statistically significant clinical parameters between patients with and without VT. Patients with VT were more likely to go on to transplant and have

worse left ventricular dilation. This pattern is not surprising since it is typically the sicker patients who develop VT. Also, there is greater substrate for reentry as the ventricular geometry undergoes further alterations with increasing dilation [56]. Our technique did outperform the presence of ventricular dilation as a marker for VT risk by correctly risk stratifying a patient with normal ventricular volumes but clinical VT and a patient with severe ventricular dilation but no VT. The computational models incorporate not just ventricular volumes but also patient specific ventricular geometry, three-dimensional tissue characterization based on patient specific LGE data, and simulated electromechanical behavior. These are all parameters not assessed by any conventional methodology. Furthermore, the lack of a statistical difference in peak troponin, phase of disease, and ejection fraction between VT positive and negative groups may further reflect the ability of our modeling process to identify at risk patients regardless of these clinical findings.

Our study was limited by the small sample size, with patients from a single institution. Out of the 18 patients originally identified for inclusion in the study, three were excluded because of underlying cardiomyopathy or channelopathy. Though these patients had myocarditis based on clinical presentation, we chose to exclude them because our simulation methodology and underlying ionic model do not account for potential mutation-driven triggered VT. Our model generation pipeline may also be adversely impacted by considering the right ventricular myocardium as all normal. This could make reentrant VT in the right ventricle less likely in our virtual electrophysiologic studies and result in our risk stratification method falsely identifying patients as not at risk. Scar though is not the only factor at play in propensity for ventricular tachycardia, as abnormal myocardial geometry itself imparts risk [56]. Our methodology does uniquely include patient-specific geometry and myocardial fiber orientation, abnormal or normal, for both ventricles.

This is the first description in pediatric medicine of the generation of complex organ scale computational cardiac models from clinical MRI data. It is also the first described use in pediatrics of such patient specific models for the performance of computational, non-invasive electrophysiology studies. Our work shows the great potential for a non-invasive, imaging based computational approach to identify children at risk for ventricular arrhythmia when afflicted with myocarditis. VT in the setting of myocarditis drastically changes resource utilization, clinical decision making, and patient outcome. As MRI is increasingly used to assist with the diagnosis of myocarditis, our novel computational methodology may have the ability to assist in early identification of at risk patients and subsequently impact clinical management and patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

a. Endocardial and epicardial contouring on short-axis MRI data. b. Myocardial tissue definition following segmentation. c. Myocardial fiber orientation. d. Action potential profile for healthy and grey zone tissue, same color legend as panel b

Fig. 2.
High-resolution ventricular heart models for all patients

Fig 3. Semi-transparent high-resolution heart models and activation maps showing simulated reentry for patients with clinical ventricular tachycardia. Arrows indicated course of reentry

Table 1

Patient data and simulation results

Patient	Age (years)	Sex	Disease state	Peak troponin I (ng/ml)	MRI LVEF (%)	Clinical Outcome	Clinical VT	Simulation Result
1	14	F	acute	12.2	20	VAD, transplant	+	+
2	10	F	chronic	0.2	18	transplant	–	–
3	17	M	acute	11.8	72	recovery	–	–
4	17	M	acute	31.0	65	recovery	+	+
5	15	M	acute	12.3	56	recovery	–	–
6	15	M	acute	1.7	57	recovery	–	–
7	14	M	acute	26.6	57	recovery	–	–
8	15	F	acute	1.6	30	recovery	–	–
9	16	M	acute	4.6	59	recovery	–	–
10	18	M	acute	5.2	56	recovery	–	–
11	16	M	chronic	0.1	11	VAD, transplant	+	+
12	15	M	acute	52.0	11	VAD, transplant	+	+

VT (ventricular tachycardia), VAD (ventricular assist device)

Table 2

Clinical MRI data and tissue type proportions based on patient ventricular tachycardia status

	VT Positive	VT Negative	p value
Patient Data (mean and standard deviation)			
MRI EDVi (ml/m ²)	193±92	95±37	p=.022313
MRI ESVi (ml/m ²)	157±101	50±38	p=.021193
MRI LVEF (%)	27±26	51±18	p=.171198
Peak troponin I(ng/ml)	23.8±22.7	8.0±8.8	p=.103727
Model Tissue Types (mean and standard deviation)			
Normal Tissue, %	78.0±3.5	80.4±3.2	p=.296672
Grey Zone, %	18.0±3.2	16.0±2.7	p=.280855
Scar, %	4.0±1.4	3.8±1.2	p=.772291

EDVi (end diastolic volume indexed to body surface area), ESVi (end systolic volume indexed to body surface area), LVEF (left ventricular ejection fraction)