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Electrocardiographic imaging-based recognition of possible induced bundle branch blocks during transcatheter aortic valve implantations

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Aims Conventional electrocardiogram (ECG)-based diagnosis of left bundle branch block (LBBB) in patients with left ventricular hypertrophy (LVH) is ambiguous. Left ventricular hypertrophy is often seen in patients with severe aortic stenosis in which a transcatheter aortic valve implantation (TAVI) frequently results in a LBBB due to the mechanical interaction of the artificial valve and the conduction system. In this feasibility study, we propose and evaluate the sensitivity of a new electrocardiographic imaging tool; the cardiac isochrone positioning system (CIPS), visualizing the cardiac activation to detect interventricular conduction patterns pre- and post-TAVI.

Methods and results The CIPS translates standard 12-lead ECG into ventricular isochrones, representing the activation sequence. It requires a patient-specific model integrating heart, lungs, and other thoracic structures derived from multi-slice computed tomography. The fastest route-based algorithm was used to estimate the activation isochrones and the results were compared with standard ECG analysis. In 10 patients the CIPS was used to analyse 20 ECGs, 10 pre- and 10 post-TAVI. In 11 cases the CIPS results were in agreement with the ECG-based diagnosis. In two cases there was partial agreement and in seven cases there was disagreement. In four of these cases, the clinical history of the patients favoured interpretation as assessed by CIPS, for the remaining three, it is unknown which method correctly classified the activation.

Conclusion This feasibility study applying the CIPS shows promising results to classify conduction disorders originating from the left anterior or posterior ventricular wall, or the septum. The visualization of the activation isochrones as well as ventricular model-derived features might support TAVI procedures and the therapy selection afterwards.

Keywords Cardiac isochrone positioning system • CIPS • 12-lead ECG • TAVI • LBBB

Introduction

The electrical activation in the ventricles spreads rapidly through the specialized His-Purkinje system, initiating the depolarization of the myocardial tissue. The His-bundle divides into several bundle branches: one branch innervates the right ventricle while the initial portion of the left branch appears between the non-coronary and right coronary aortic cusps, as a ribbon-like sub-endocardial structure running inferiorly and slightly anteriorly with a width varying from 6 to 10 mm.[1] This left branch quickly fans out in sub-endocardial fasciculi arranged into two or three main radiations,[1] innervating larger parts of the endocardial left ventricle. A conduction disorder in any of these branches could result in an impaired cardiac output due to delayed electrical activation of large parts of the ventricles. Left bundle branch block (LBBB) corresponds to the dysfunction of all bundles in the left ventricle, resulting in a 70 to 80 ms prolongation of the QRS complex. The consequences for the electrical activation sequence, from right to left, can finally result in cardiac pump failure, and thus cardiac output.

The current electrocardiogram (ECG) criteria are not specific enough to reliably diagnose a LBBB from standard 12-lead ECG-recordings.[2] One of the possible reasons for a false-positive

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What's new?

- Cardiac isochrone positioning system uses the standard 12-lead electrocardiogram (ECG) and multi-slice-computed tomography images to estimate ventricular activation isochrones.
- Classification of left bundle branch blocks (LBBBs) from activation isochrones visualized on patient-specific cardiac models might improve the identification of various types of left ventricular conduction abnormalities.
- Transcatheter aortic valve implantation (TAVI) procedures result in LBBB in up to 30% of patients. As the left ventricle of TAVI patients is almost always hypertrophied, limiting the specificity of conventional electrocardiographic (ECG) criteria for LBBB.
- Improving diagnosis of LBBBs could help guiding to select further treatment strategies for this group of patients.

detection of a LBBB is the fact that some patients have enlarged (hypertrophic) left ventricles, which can result in similar QRS morphological changes.[2] Furthermore, endocardial mapping studies in patients diagnosed with LBBB showed activation patterns with multiple initiation sites in the left ventricle. Such activation patterns are not consistent with the LBBB activation pattern.[3,4] In patients with severe aortic valve stenosis, the left ventricle is often, if not always, structurally remodelled, although in many cases the QRS complex has a normal duration ($<$100 ms).[5,6]

Recently, transcatheter percutaneous aortic valve implantations (TAVIs), with a bioprosthetic valve attached to a stent frame, have become a widely used treatment option in complex patients in which surgery is not an option. These TAVI procedures induce LBBB in $\sim$10–30% of the patients, most likely related to the mechanical interaction of the frame of the implanted valve and the conduction system.[5,7–9]

In this feasibility study, changes in the development of conduction disorders are observed and detected by comparing the pre- and post-implantation activation sequences derived from 12-lead ECG monitoring during the TAVI procedure. The main objective was to investigate the applicability of the recently developed cardiac isochrone positioning system (CIPS) to differentiate between various types of intra-ventricular conduction disorders: partial-, complete-, left-, or right bundle branch blocks (BBBs).[10] The CIPS translates the 12-lead ECG into activation isochrones and shows them as color maps onto the surface of patient-specific derived models of their heart from multi-slice computed tomography (MSCT) or magnetic resonance imaging (MRI) scans using a specifically developed and dedicated morphing computerized software tool.[10,11] From these isochrones, the type of BBB can be identified.

Methods and patient population

The block diagram of the CIPS is shown in *Figure 1*. The input to the CIPS software is MSCT data and the 12-lead ECG. From the image data, patient-specific models are created which are used to compute the ventricular activation isochrones.

The cardiac isochrone positioning system

This method has been previously described.[10] Briefly, the method has four major components:

(i) Cardiac current source model linked to cardiac electrophysiology
(ii) Volume conductor effects:
  (a) proximity effect, spatial orientation of the nine ECG electrodes
  (b) inhomogeneous volume conductor
(iii) Patient's specific geometry from computed tomography (CT) (*Figure 1*),
(iv) Rough- and fine tuning of the activation isochrones localization
  (a) The fastest route-based initial estimate of cardiac activation
  (b) Optimization procedure

The first component, the cardiac current source model, is the equivalent double layer (EDL). The EDL represents the currents generated by the cardiac tissue during activation and recovery, which is equivalent to the currents generated by all coupled myocardial cells as recorded at endo- and epicardial surfaces.[12,13] Consequently, the EDL is referred to the localization at the endo- and epicardial surface of the myocardium. For any position (node) on the triangulated ventricular surface, the time course of the local source strength is taken to be proportional to the transmembrane potential of the nearby myocytes.[14,15] The second component accounts for the volume conductor effects, being: (i) proximity and spatial orientation of the nine ECG electrodes and (ii) the differences in conduction properties of the various tissues. The proximity effect and spatial orientation are determined by the solid angle of the active cardiac tissue as observed from the ECG electrodes.[16] The solid angle accounts for the fact that ECG waveforms of electrodes close to the heart are dominated by the cardiac tissue underneath depending on the direction of the wave front. Previous studies indicated that an appropriate volume conductor model requires the incorporation of the heart, blood cavities, lungs, and thorax.[17,18] In this study, the conductivity values σ assigned to the individual compartments were: thorax and ventricular muscle: 0.2 S/m, lungs: 0.04 S/m and blood cavities: 0.6 S/m. The mathematical method used to solve this volume conductor problem in a numerical way is referred to as the boundary element method (BEM).[19,20] With the BEM, a transfer matrix B can be computed taking into account the full complexity of the discretized volume conductor model. For the potentials at thorax node ℓ of the 12-lead electrodes is defined by

$$\phi(t;\ell) = \Sigma_n B(\ell, n) S(t; \delta_n, \rho_n) \quad (1)$$

in which $S(t; \delta_n, \rho_n)$ is the local time-dependent EDL source strength, and $B(\ell, n)$ is the BEM-derived transfer function relating the contribution of S at node n to the potentials ϕ at thorax node ℓ.

The third component relates to patient-specific geometries of the heart, lungs, and thorax derived from MSCT (*Figure 1*). Previous studies have shown the importance of patient-specific models.[21,22] These models were created with a new morphing software.[23] With this software the boundaries of all relevant tissues were identified manually. For the ventricles these boundaries are the left- and right endocardium, epicardium, aorta, and pulmonary artery. To capture

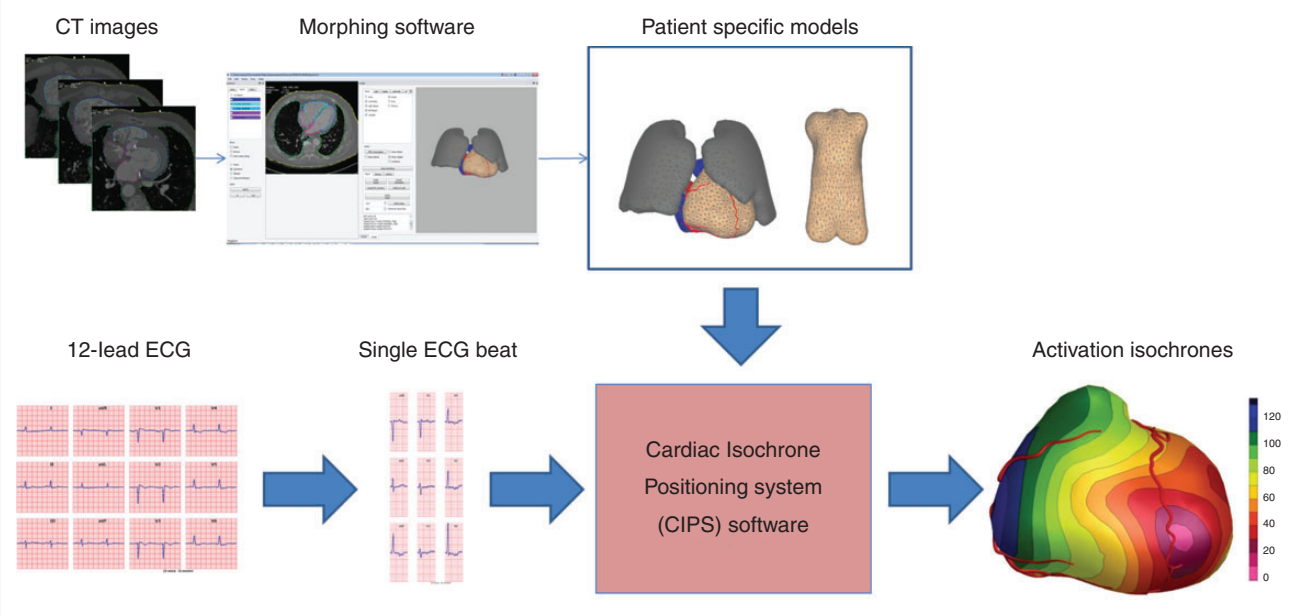

Figure 1 Block diagram of the activation based cardiac isochrones positioning system (CIPS) method. Inputs are: (i) the CT (MSCT) images and (ii) the 12-lead ECG. The CT images are used to create patient-specific models of the heart, lungs, and thorax. From the 12-lead ECG a single beat is selected. Only the signals referenced to the average of Vr, Vl, and Vf are used by the CIPS software to estimate the activation isochrones.

the spatial orientation from the 12-lead electrodes, the epicardium and endocardium, lungs, and thorax are morphed to match the manual drawn contour points—patient-specific geometries.

The fourth component uses the previous three components to position the activation isochrones on the endo- and epicardial ventricular surfaces. The rough tuning step is an adapted version of the fastest route to obtain an electrophysiological-based initial estimate of the activation sequence as described previously.[10,24] In short: In this application multiple foci are determined using the fastest route algorithm. It is anticipated that the activation is initiated from multiple sites of the Purkinje system, located in the lower 70% from the endocardial surface. For each node in this endocardial Purkinje area, an activation sequence is computed using a propagation velocity of 0.8 m/s. The first estimate of the activation isochrones is the one with the highest correlation between the actual measured ECG and the model-derived ECG. In the next iteration an extra focus is added. The activation sequence is computed by the 'first come, first served' principle. This procedure is then repeated until there is no increase in correlation found. The final activation isochrones are obtained by a Levenberg–Marquardt-based optimization procedure in which the rough tuned activation isochrones are tuned to obtain matching ECGs.

Patient data

From our database, 10 elective TAVI patients who showed major ECG changes between pre- and post-TAVI procedures were analyzed with CIPS. The study group involved elderly patients (3 females, 7 males) with an average age of 77 $\pm$ 9 years and as further medical history: coronary disease,[8] Ventriculoseptal defect (VSD) repair,[1] atrioventricular block,[2] and atrial arrhythmias[3] (*Table 1*). The study was approved by the local ethics committee and all patients signed informed consent for the procedure. According to the institutional standard protocol for TAVI procedures, all patients underwent an MSCT-scan pre-TAVI. This image data were used to create the patient-specific heart-, lung-, and thorax models. The volume of the ventricular myocardial model can be computed. From these model-derived myocardial volumes the left ventricular mass (LVM) was estimated (see *Table 1*). For 6 out of the 10 patients, the LVM was significantly increased, i.e. the LVM was not within the normal range reported by Cain *et al.*[26] Additionally, the LVM was corrected for the body surface area (BSA), using the Gehan method to compute the BSA.[27]

Analysis

Representative 12-lead ECG beats were recorded just minutes before the valve implantation, at the cathlab table, and at the end of the TAVI procedure, before the patient left the cathlab table, and used to estimate specific ventricular activation isochrones (*Figures 2–4*). The 12-lead ECG electrodes were placed at the standard positions by the same highly experienced operator for all patients (AMM). The fact that some patients could have scar tissue was not taken into account in this study (*Table 1*).

The activation isochrones were visually inspected and qualified. If only initial activation was found in the right ventricle, the activation was qualified as LBBB. When only activation sites were found in the right chamber and left septum (not related to the right-sided activation), the pattern was qualified as *fascicular block*. The *left anterior fascicular block* (LAFB) or left posterior fascicular block (LPFB) showed delayed activation in the anterior wall, respectively posterior wall. The results of CIPS were compared with standard 12-lead ECG analysis performed by three blinded experts on ECG interpretation. For two ECG cases one of the three experts disagreed with the other two (see *Table 2*). Left bundle branch block was

Table 1 Description of medical history of the 10 TAVI patients

Pat. #	Medical history	Age	Weight (kg)	Height (cm)	Gender	LVM (normal LVM (25)) (g)	LVM/ BSA
1	• Ventriculoseptal defect correction, aorta insufficiency (1982) • Atrial flutter (2011)	58	60	174	M	275 (183)*	161
2	• Stenosis mid right coronary artery (RCA), proximal, distal LCx, and intermediate left anterior descending artery (LAD) (2012) • Third-degree AV block (2012)	87	79	169	M	170 (163)	87
3	• Non-ST infarct (2008) • PCI LCX, right dominant, diffuse LAD sickness (2011) • RCA, failed PCI (2012)	76	81	175	M	198 (163)	99
4	• AAI pacemaker • Right dominant significant stenosis prox and mid LAD • LCX wall irregularities	86	74	157	F	238 (129)*	131
5	• LAD 50%	80	90	187	M	232 (163)*	107
6	• LVH	81	40	150	F	137 (129)	105
7	• Inferior infarct (1980) • PCI LAD and heart failure (1981) • Sick sinus syndrome, DDD pacemaker (2009) • Diffuse sick RCA (three stents) en PCI LAD (2012)	86	61	172	M	255 (163)*	149
8	• Right dominant • LAD and LCX irregularities	67	70	175	M	220 (173)*	119
9	• Non-stemi, PCI LCX (2010) • Ballooning aorta valve (2012) • Third-degree AV block	73	87	178	M	400 (163)*	192
10	• Mitral stenosis, (1993/1998 prosthesis) • Atrial fibrillation, chronotropic incompetent, His ablation DDDR pacemaker (2002)	78	64	162	F	158 (129)	92

The LVM was obtained from the CT-derived model, using a specific gravity for cardiac tissue of 1.05 g/ml and assuming one-fourth of the total cardiac wall volume is taken by the right free wall.[25] In brackets the age-matched normal values are listed.[26] The patients with significant higher values for LVM are marked with an asterisk. Additionally, the BSA correct LVM values are listed on the last column. The BSA was computed using the Gehan method.[27] LCx, left circumflex; PCI, percutaneous coronary intervention.

defined according to the American heart association recommendations.[28] In short: QRS duration >120 ms, no *Q*-waves in I, V5, V6 and broad notched *R*-waves in I, aVL V5, V6. Left ventricular hypertrophy was diagnosed if no notch was present and the *R*-wave in aVL exceeded 1.7 mV.

Results

For 11 of the 20 ECG (10 pre- and 10 post-TAVI) recordings, the qualification of CIPS was in agreement with the qualification as given by the experts (*Table 2*). A typical example of a patient developing LBBB's post-TAVI is presented in *Figure 2*. In two cases CIPS was partially in agreement with the expert. For Patient 5 the expert qualified the ECG as normal prior to the procedure; however, CIPS showed normal right ventricular activation with a delayed left chamber (onset activation after 30–40 ms). A similar pattern was also found in Patient 8 (*Table 2*), but now additionally with a LAFB. For seven ECGs the qualifications between the expert and the CIPS did not match. However, in favour of CIPS in two of these patients (Patients 1 and 10), i.e. four cases (two pre- and two post-TAVI), the CIPS findings were corroborated by the cardiac history of these particular patients (*Table 1*). For Patient 9 the disagreement between ECG experts and CIPS is shown in *Figure 3*. This patient had a major increase in left ventricular wall mass (LVM), 400 g where 163 is normal (*Table 1*). This increase was correctly diagnosed by the ECG experts as LVH. However, no conduction disorders were detected by the experts, whereas the activation isochrones computed by CIPS showed a fascicular block pattern pre-TAVI and a LBBB pattern post-TAVI (*Figure 3*).

The first patient (*Figure 4*) was qualified by the expert as RBBB, i.e. the right chamber is activated from the left chamber. However, the CIPS-based isochrones show initial activation in the left (0 ms) and right (40 ms) free wall. This initial activation of the right chamber is not related to the activation from the left chamber and thereby inconsistent with a true RBBB finding. The CIPS-derived activation isochrones were consistent with the fact that this patient had a VSD repair 30 years earlier, most likely causing late septal activation. In Patient 10, the activation qualification was obscured by the fact that the heart was paced. The CIPS correctly identified initial activation in the posterior/inferior wall of the right ventricle (pacing site), whereas the expert identified the activation as normal with QRS widening.

Discussion

Identification of LBBB's using the conventional standard analysis method by interpreting 12-lead ECG recordings can be ambiguous.

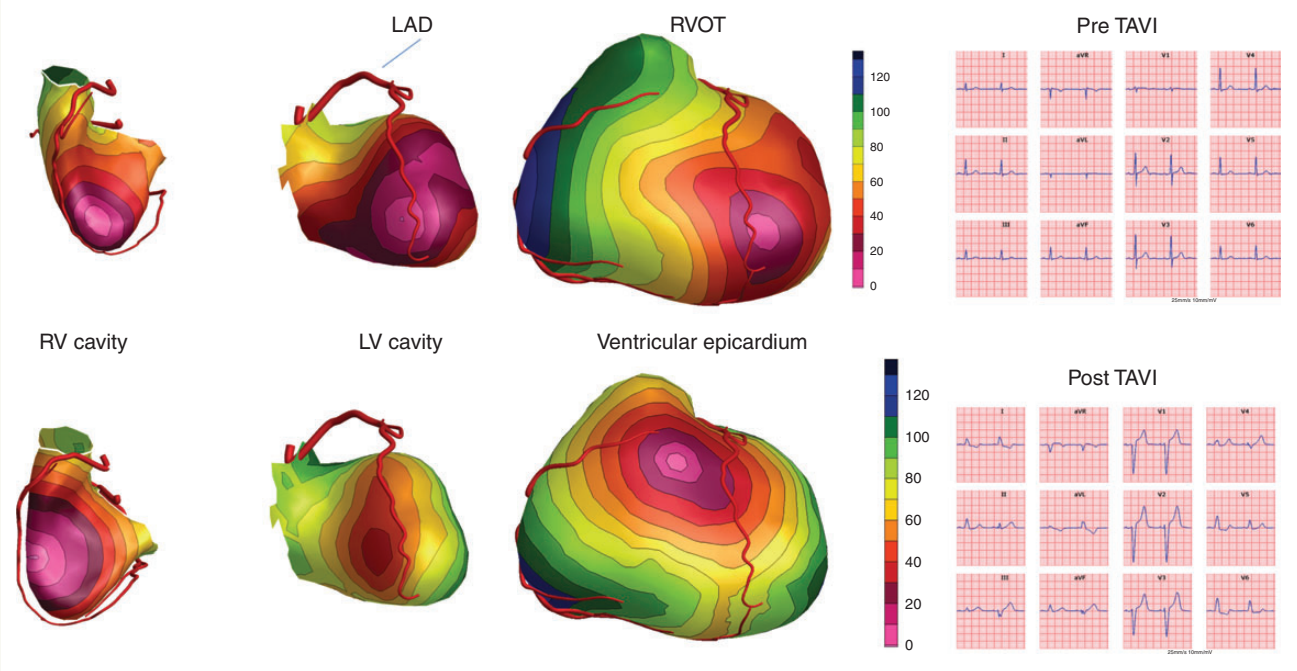

Figure 2 Cardiac isochrones positioning system results for Patient 2. Prior to the TAVI procedure normal activation was found (top panels) and a complete LBBB pattern post-TAVI (bottom panels). On each row: the isochrones are shown on: (from left to right) the right endocarial cavity, the left endocardial cavity, and ventricular epocardium (middle) estimated from the 12-lead ECG. The left anterior descending artery (LAD) is shown for orientation purposes. Iscochrones are drawn every 10 ms.

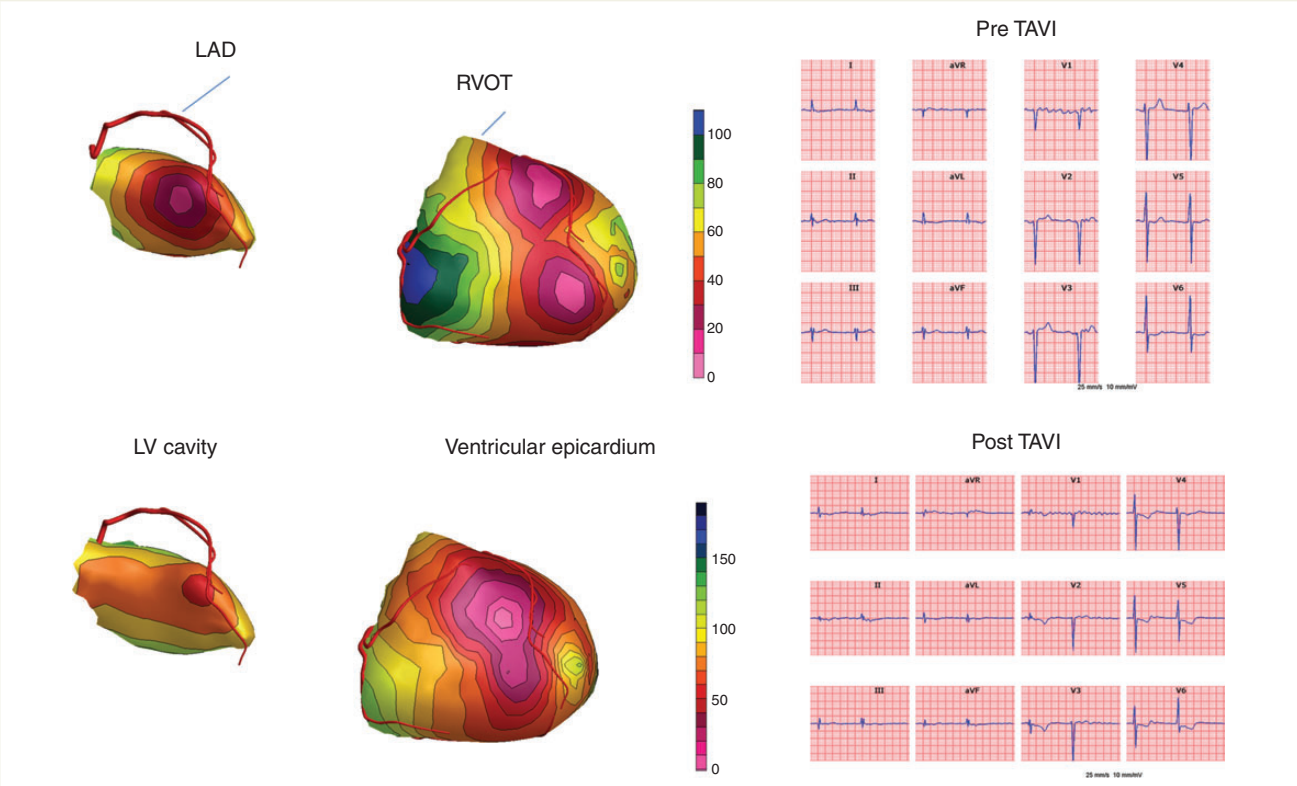

Figure 3 Cardiac isochrone positioning system results for Patient 9. Prior to the TAVI procedure the activation is shown to be earliest in the right chamber, immediately followed by early left sepatal activation (top panels). Post-TAVI (bottom panels) the right ventricle is still activated early, but the early activation in the left septum has disappeared. On each row, the isochrones are shown on the left endocardial cavity (left) and ventricular epocardium (middle) estimated from the 12-lead ECG. The aorta is shown for orientation purposes. Iscochrones are drawn every 10 ms.

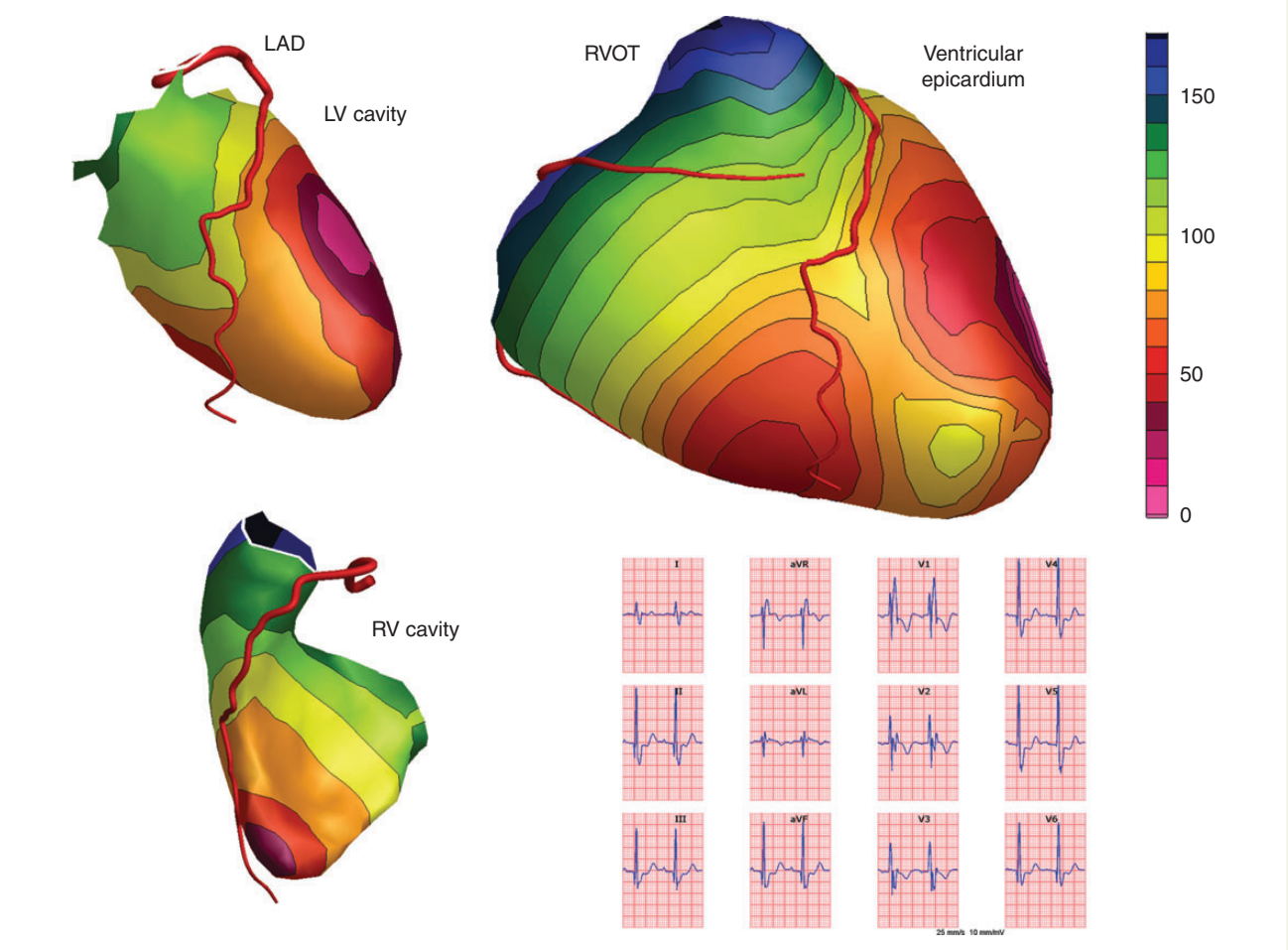

Figure 4 Cardiac isochrone positioning system results for Patient 1. This patient was identified as a RBBB patient according to the expert's ECG-based diagnoses. The CIPS created model showed activation initiation in the left lateral wall (onset QRS = 0 ms), and at 40 ms in the right apex. No initial activity was found in the septum, which might have been caused by the fact that the patient had a VSD repair in 1982. The left ventricular cavity and the ventricular epicardium are shown in an AP view, the right ventricular cavity is shown in an oblique view showing the right septal wall. The LAD is shown for orientation purposes. The activation isochrones are drawn every 10 ms.

The presented CIPS visualization method might be a valuable additional tool to optimize diagnosis and interpretation of ventricular activation abnormalities. Patients undergoing TAVI procedures are an exceptional cohort as they have often multiple, complex cardiac pathologies. Their electrical system may undergo considerable changes periprocedural. This feasibility study shows that: (i) The CIPS can be applied to study this particular patient cohort using standard 12-lead ECG and MSCT data (*Table 2*) and (ii) it showed in several cases a different diagnosis of the heart activation abnormalities of which in four cases the CIPS results were close to the underlying medical cardiac history of those particular patients (1 and 10) when compared with the expert analysis (*Figure 4*). However, in two patients (Patients 4 and 9 in three pre- and post-TAVI ECGs) the results by both methods were contradicting. The detection of conduction disorders in Patient 9 with severe LVH by CIPS (*Figure 3*) needs to be validated by another gold standard than the ECG. Previous studies showed that the detection of conduction disorder from the ECG is unreliable (*Table 2* and (ii)).

Cardiac isochrone positioning system might thus be helpful to interpret ventricular activation changes as detected by standard 12-lead ECG recordings, especially in patients with enlarged ventricles.[2] Moreover, visualization of the cardiac electrical activation isochrones onto a patient-specific model of the heart could potentially be helpful to identify the type of activation abnormality. The correct classification of the conduction disorder will support the correct treatment strategies post-TAVI, such as for example the implantation of a permanent pacemaker in case of partial LBBB.[29]

Modelling the myocardium

This feasibility study explored the possibilities to apply this method in a specific patient population in which LVH is common and conduction disorders are often induced due to the treatment they receive, e.g. TAVI. A major advantage of CIPS is the personalized reconstruction of the ventricular myocardium from standard collected MSCT data. The fact that the heart is structurally remodelled is taken into account by the method.

Table 2 Pre–post TAVI procedure results comparison

Pat. #	Pre-TAVI		Post-TAVI		LVM > normal (*Table 1*)
	From 12 lead ECG	Activation isochrones	From 12 lead ECG	Activation isochrones	
1	RBBB LVH	Septal block	RBBB LVH	Septal block	X
2	NA	NA	LBBB	LBBB	
3	Incomplete LBBB	Incomplete LBBB (LAFB)	LBBB	FB	
4	NA, Brugada	LAFB	Incomplete RBBB	RBBB + LAFB	X
5	NA	RV normal with delayed LV septum	LBBB	FB	X
6	LAFB LVH	LPFB	LBBB LVH	LBBB	
7	Incomplete LBBB	FB check	NA	LAFB	X
8	NA	NA	LBBB LVH	LAFB, delayed LV	X
9	No block LVH	FB	LVH	LBBB	X
10	Atypical LVH with QRS widening	Pacing RV posterior wall	Atypical LVH with QRS widening	(In)complete LBBB, borderline case	

LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; BS, Brugada syndrome; FB, fascicular block; only the septum gets activated; NA, normal activation. Colours show agreement of the methods: green—agree, orange—partially agree, red—disagree. The ECG experts disagreed on the pre-TAVI ECG of Patient 8 (stripped, NA:2 and LVH:1) and on the post-TAVI ECG of Patient 9 (LVH: 2 and no block (ischaemia):1).

Several studies investigating conduction disorders after TAVI treatment indicated that many factors play a role in the development of transient conduction disorders, including patient cardiac history, procedural characteristics, and the implanted valve type.[5] For example, an important related implantation factor such as the location and the depth of the implanted bioprosthesis framework in relation to the left ventricular outflow tract could play a major role.[5,6,8] Other factors, such as LVM (see *Table 1*), septal wall thickness, outflow direction of the aorta, or the remodelling of the ventricles over time could be derived from the used models created by CIPS. The model-derived features as well as the activation isochrones might be helpful to plan and optimize TAVI procedures.

Electrocardiogram versus activation isochrones

The classification of the activation isochrone patterns has not been standardized. In this study, we classified four types of left sided block patterns, LAFB or LPFB, fascicular block (FB, septal activation only), and complete block (LBBB). This classification agrees better with the anatomical distribution of the Purkinje system into three major sub-branches.[1] The used classifications (LAFB, LPFB, LB, and LBBB) cannot directly be translated into the classifications derived from the ECG. As such our method might enable a more anatomical-based classification, because the activation isochrones are registered to anatomical locations of the ventricle.

In seven pre- and post-TAVI ECG analysis, the results of the expert and CIPS did not (completely) match (e.g. in Patients 4, 5, 8, and 9). Due to the retrospective setup of the study, two factors might contribute to these mismatches: (i) the fact that scar tissue was not taken into account, and (ii) the exact location onto the thorax of the nine ECG electrodes in every patient was unknown. Both factors introduce systematical modelling errors, and consequently deviations in the estimated activation sequence. The electrical function of scar tissue is impaired, whereas in the current setup CIPS assumes healthy cardiac tissue. This altered electrical function needs to be addressed when modelling the myocardium. We assumed that the standard 12 lead ECG positions were applied; however, the electrodes might have been placed somewhat differently due to the constraints determined by the TAVI procedure in the catheterization laboratory. Such lead 'misplacement' would influence the resulting activation isochrones. The presence of scar tissue in some of the patients (*Table 1*) results in additional modelling errors.[30] In the current setup, the ventricular model assumes healthy myocardial tissue for both ventricles. These confounding factors, possible lead misplacement and/or the presence of scar tissue, might explain the disagreements within Patients 4–6 and 9. For these particular cases, an independent confirmation of the underlying activation sequence is required, which can only be acquired via intracardiac ECG measurements.

Limitations and future work

This retrospective feasibility study incorporates only a small cohort of patients and larger studies are warranted to evaluate this method at a larger clinical scale. Although the initial results are promising, our concept needs further validation and the exact clinical usefulness needs to be established by a prospective study. The interpretation differences between the expert and the CIPS can only be resolved in the future by an independent gold standard, for instance endocardial or epicardial mapping. However, mapping may be difficult during a TAVI procedure. Although the ECG expert was

blinded in this feasibility study to the CIPS results, the CIPS observer was not blinded to the ECG.

In this study, we did not take the presence of scar tissue into account. In a future study, the influence of the scar tissue on the estimated isochrones needs to be determined. The gold standard for the localization of scar tissue is delayed enhancement MRI, which might be contraindicated for the patients with such complex cardiac history. Cardiac isochrone positioning system might also be a valuable tool to identify patients who might benefit from cardiac resynchronization therapy. Future studies integrating mechanical parameters such as left ventricular ejection fraction together with electrical activation disorders are warranted.

Conclusion

This feasibility study describing and applying the CIPS shows promising results to classify conduction disorders originating from the left anterior or posterior ventricular wall, or the septum. The visualization of the activation isochrones as well as ventricular model-derived features might support TAVI procedures and the therapy selection afterwards.

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Conflicts of interest: none declared.

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