

In Silico Trials for Sex-Specific patient Inclusion Criteria in Cardiac Resynchronization Therapy

Shuang Qian^{1,2}, Devran Ugurlu^{1,2,3}, Elliot Fairweather², Richard E Jones^{1,4,5}, Hassan Zaidi², Sanjay Prasad^{1,4}, Brian P Halliday^{1,4}, Daniel Hammersley^{2,4,6}, Gernot Plank^{7,8}, Edward Vigmond^{9,10}, Cristobal Roderio¹, Abdul Qayyum¹, Derek Bivona¹¹, Kenneth C Bilchick¹¹, Christopher A Rinaldi², Alistair Young², Pablo Lamata², Martin Bishop², Steven Niederer^{1,12}

¹National Heart and Lung Institute, Imperial College London, London, UK

²Department of Biomedical Engineering, School of Imaging Sciences and Biomedical Engineering, King's College London, London, UK

³Alan Turing Institute, British Library, 96 Euston Rd, London, UK

⁴Cardiovascular Magnetic Resonance Unit, Royal Brompton and Harefield Hospitals, Guy's and St Thomas' National Health Service Foundation Trust, London, UK

⁵Anglia Ruskin School of Medicine & MTRC, Anglia Ruskin University, Chelmsford, UK

⁶King's College Hospital NHS Foundation Trust

⁷Gottfried Schatz Research Center, Division of Biophysics, Medical University of Graz, Graz, Austria

⁸BioTechMed-Graz, Graz, Austria

⁹University of Bordeaux, CNRS, Bordeaux, Talence, France

¹⁰IHU Liryc, Fondation Bordeaux Univ, Talence, France

¹¹Department of Medicine, University of Virginia Health System, Charlottesville, VA

¹²Division of Cardiovascular Medicine, Stanford Cardiovascular Institute, Stanford Univ., CA, USA

Corresponding address: Dr S Qian, 3rd Floor, ICTEM building, Hammersmith Campus, London, W12 0NN, UK (s.qian23@imperial.ac.uk)

Abstract

Cardiac resynchronization therapy (CRT) guidelines are based on clinical trials with limited female representation and inconsistent left bundle branch block (LBBB) definitions. Conventional QRS duration (QRSd) criteria show variable diagnostic accuracy between sexes, partly due to differences in heart size and remodeling. We evaluated the influence of sex, heart size, LBBB, and conduction delay on QRSd and assessed the diagnostic performance of conventional and indexed QRSd criteria using a population-based modelling approach. Simulated QRSd were derived from electrophysiological simulations conducted in 2627 UK Biobank healthy participants and 359 patients with ischemic heart disease, by modelling LBBB and normal activation combined with/without conduction delay. QRSd criteria under-selected LBBB females and over-selected non-LBBB patients. Indexing by LVEDV and LV mass reduced sex disparities but increased the over-selection in non-LBBB patients. Height-indexed QRSd effectively resolved sex differences and maintained low non-LBBB selection rates, demonstrating superior performance and potential for more equitable CRT selection. These results uncover a key mechanistic driver of sex differences in LBBB detection that may contribute to CRT outcomes and underscore the importance of incorporating sex-specific considerations into updated CRT guidelines to ensure equitable and effective treatment.

Introduction

Cardiac Resynchronization Therapy (CRT) is a treatment that improves the cardiac function in patients with heart failure and left bundle branch block (LBBB). A key clinical biomarker used for selecting eligible patients is QRS duration (QRSd), which is a reading on electrocardiograms (ECGs), reflecting the time taken for ventricular activation, important for assessing the health of the heart's conduction system. While CRT has been widely used and helped many patients, about 30% of patients do not show expected clinical improvements¹. One factor that may contribute to this variation in outcomes is biological sex. While some studies, such as CARE-HF (Cardiac Resynchronization in Heart Failure)², reported no significant sex differences, most clinical evidence suggests that women demonstrate higher response rates to CRT, compared to men, particularly at shorter QRSd³.

The mechanisms underpinning these sex differences in CRT response remain poorly understood. Previous clinical studies have proposed that differences in heart sizes and QRSd may partly explain the observed variation⁴. This was supported by our prior large-scale modelling study⁵ which showed how the shorter QRSd in women can be entirely explained by smaller heart sizes, without intrinsic differences in myocardial conduction velocity. Various indexed QRSd criteria, such as by cardiac structural metrics including heart volumes and mass, or body habitus measures including height, have been proposed to resolve these differences and improve patient selection. But these studies have largely been examined in small clinical cohorts and only considered patients who met the conventional/unindexed QRSd inclusion criteria³. As a result, such analyses may be biased toward showing that women who meet both conventional and indexed criteria benefit from CRT, while overlooking potential responders including both men and women who meet indexed criteria but not conventional criteria.

In addition to structural remodelling, functional remodelling also plays a vital role in varying QRSd in CRT patients/candidates. Functional remodelling can be generally categorised by two pathological processes: (1) left bundle branch block (LBBB), resulting in electrical desynchrony, and (2) slowed myocardial conduction due to the presence of scarring or myocardial fibrosis, ionic remodelling or gap junction down-regulation⁴, which can both lead to the conduction delay and manifest as QRSd prolongation. Previous studies demonstrated that patients with LBBB generally derive greater benefits from CRT compared to those without it⁶. To identify LBBB patients, various criteria based on QRS morphology in the electrocardiograms have been proposed, which have led to considerable variability in patient stratification⁷, while the QRSd criteria remain the gold-standard clinical biomarker for identifying CRT patients. However, the relative impacts of these distinct pathological substrates, or their combinations on QRSd in different sexes, remain poorly understood. Furthermore, it is also unknown how these distinct pathological substrates affect the diagnostic efficacy of the current conventional QRSd and indexed QRSd in different sexes. Here we assess whether QRSd-based criteria are complementary to morphology-based criteria by improving sex-equitable identification of patients with a canonical LBBB substrate.

Computational models offer a unique platform for dissecting the impact of different pathological changes on QRSd in a controlled manner. By leveraging patient-specific anatomical models derived from clinical imaging, it is possible to prospectively evaluate the diagnostic performance of various conventional or indexed QRSd criteria under different pathological scenarios. A key limitation of prior studies is their focus on patients who already met conventional QRSd criteria, rather than considering a broader population. Here, we introduce a novel approach using virtual cohorts, which

allows for the exploration of a wide distribution of cases, including those who may not have met conventional inclusion criteria.

In this study, we hypothesize that the sex difference in CRT response is influenced by sex-dependent diagnostic accuracy for patients with different pathological changes, combined with the known factor of heart size differences. To test this, we prospectively evaluate the efficacy of conventional QRSd and indexed QRSd criteria for stratifying virtual LBBB and non-LBBB patients in different sexes under varying degrees of pathological changes. The simulated scenarios include LBBB and normal activation, in combination with/without slow myocardial conduction. These simulation scenarios were applied to patient-specific models developed from two large-scale cohorts: (1) healthy volunteers from the UK biobank (UKBB), representing anatomically healthy hearts, and (2) patients with ischemic heart disease (IHD), representing diseased anatomies with structural modelling. By expanding beyond conventional inclusion criteria and leveraging population-level models, this study provides new insights into the sex-specific efficacy of CRT selection criteria and their implications for optimizing patient outcomes.

Results

Basic patient characteristics

Table 1 summarizes participant characteristics for the healthy cohort (free from cardiovascular disease (CVD)) from UKBB and the IHD cohort. Females comprised 57% of the healthy cohort and 12.5% of the IHD cohort. Significant sex differences were observed in all cardiac structural metrics such as left ventricular end-diastolic volume (LVEDV) ($P < 8.1 \times 10^{-6}$), with the mean LVEDV and LV mass in IHD cohort being approximately 30% larger than those in the healthy cohort. Left ventricular ejection fraction (LVEF) differences by sex were non-significant in both cohorts, although the mean LVEF was lower in the IHD cohort (male: $45.2 \pm 16.0\%$ vs $49.7 \pm 16.0\%$) compared to the healthy cohort (male: $55.0 \pm 6.1\%$ vs $57.6 \pm 5.4\%$).

QRSds during sinus rhythm were shorter in females compared to males in the healthy cohort (84 ± 11.3 ms vs 92.5 ± 12.5 ms, $P = 8 \times 10^{-90}$). Similarly, in the IHD cohort, females have shorter QRSds than males (100.8 ± 26.5 ms vs 106.9 ± 22.5 ms, $P = 0.01$).

In the IHD cohort, there was no significant difference between sexes in the extent of core infarct mass ($P = 0.85$) or the affected territories ($P = 0.5$).

	UKBB: Male (n=1125)	UKBB: Female (n=1502)	P value	IHD: Male (n=314)	IHD: Female (n=45)	P value
Age (year)	61.2 ± 7.6	60.3 ± 7.3	0.001	64.2 ± 10.0	63.0 ± 9.1	0.34
Weight (kg)	83.0 ± 13.0	68.4 ± 12.3	9.8×10^{-163}	84.2 ± 15.4	70.4 ± 12.0	1.8×10^{-8}
Height (cm)	176.5 ± 6.4	163.1 ± 6.3	$< 1 \times 10^{-16}$	174.2 ± 8.3	162.5 ± 6.8	3.9×10^{-17}
BMI (kg/m ²)	26.6 ± 3.7	25.7 ± 4.4	1.9×10^{-14}	27.8 ± 4.9	26.7 ± 4.6	0.21
Left ventricular end- diastolic	156.1 ± 29.8	119.1 ± 19.9	9.5×10^{-218}	222.3 ± 81.5	171.2 ± 66.4	8.1×10^{-6}

volume (LVEDV/mL)						
Right ventricular end-diastolic volume (RVEDV/mL)	158.7±29.4	114.8±20.3	4.3×10^{-265}	157.3±42.3	120.6±38.5	2.3×10^{-8}
Left ventricular mass (LV mass/g)	127.3±20.2	91.1±13.1	$< 1 \times 10^{-16}$	162.2±51.3	123.8±42.7	3.6×10^{-7}
Left ventricular ejection fraction (LVEF/ %)	55.0±6.1	57.6±5.4	0.46	45.2±16.0	49.7±16.0	0.11
QRS duration (QRSd) measured at sinus rhythm	92.5±12.5	84±11.3	8×10^{-90}	106.9±22.5	100.8±26.5	0.01
Core infarct mass % of LV				16.5±9.9	16.3±10.4	0.85
Scar Predominant territory						0.5
Anterior				138 (43.9%)	22 (48.8%)	
Lateral				118 (37.6%)	17 (37.8%)	
Inferior				43 (13.7%)	6 (13.3%)	

Table 1: Basic characteristics of the healthy cohort from the UK biobank (n=2627) and the clinical cohort of patients with IHD (n=359).

Summary statistics of simulated QRSd in four pathological scenarios

Four pathological scenarios were simulated for each patient-specific anatomical model and the resultant QRSd were calculated. Figure 1A showed QRSd simulated using healthy anatomies from UKBB with normal and LBBB activation. A 25% increase in QRSd was observed with LBBB activation (78.04±5.92 vs 97.56±7.55 ms, P<0.0001). Males exhibited longer QRSd than females in both groups (normal: 82.1±4.9 vs 75±4.7 ms and LBBB: 102.2±7.2 vs 93.7±5.1 ms, both P<0.0001). In scenarios involving additional slowed myocardial conduction (Figure 1B), QRSd were further prolonged (120.1±9.6 vs 145.5±12.9 ms, P<0.0001), with preserved sex-specific differences (healthy: 126.6±8.6 (male) vs 115.2±7.1 ms and LBBB: 153.4±12.9 (male) vs 139.5±9.2 ms, both P<0.0001). Using IHD anatomical models, mean QRSd were approximately 8 ms longer compared to healthy models, with slow conduction adding an additional 11 ms prolongation in the mean QRSd (Figure 1 C, D). Consistent sex-specific differences were noted.

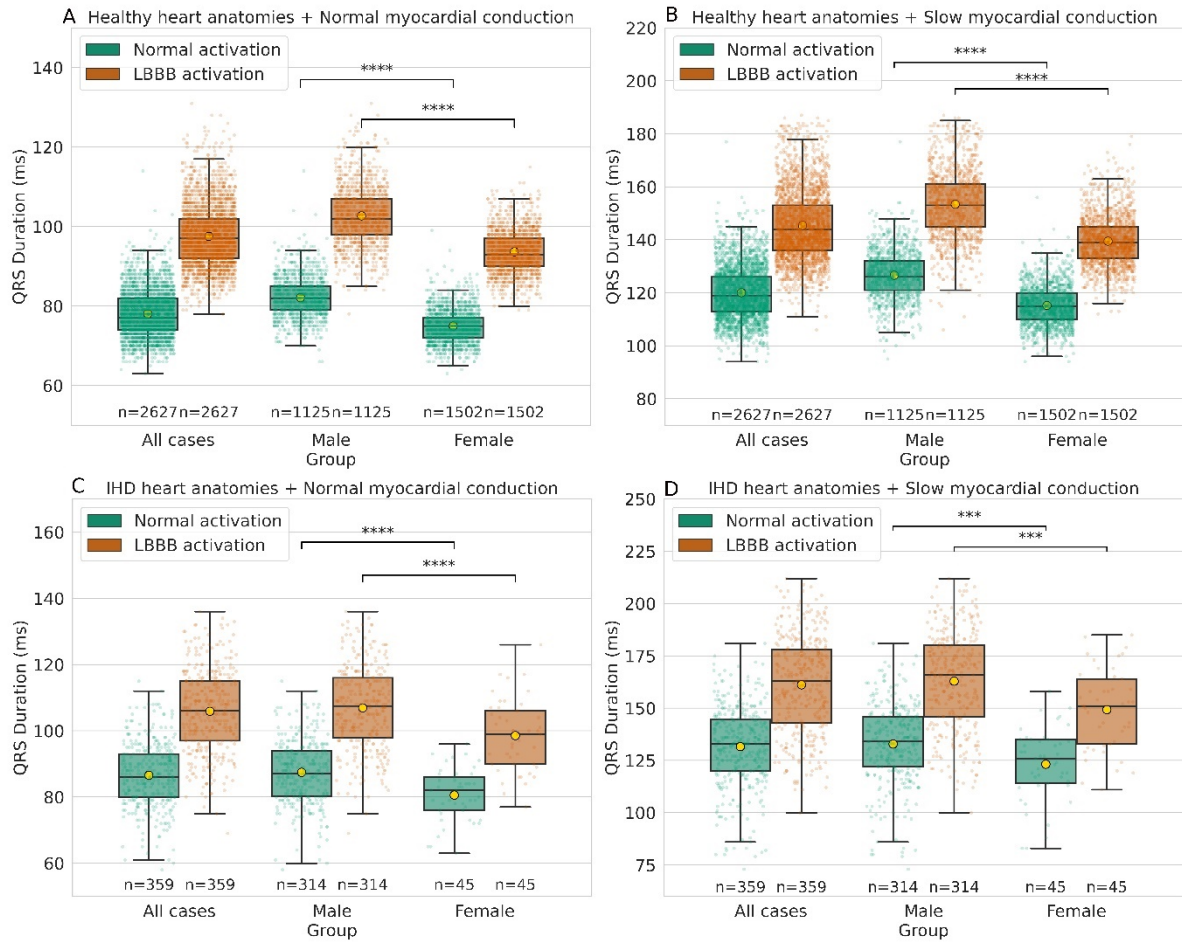


Figure 1: Comparison of QRSds simulated in four pathological scenarios of both sexes in both healthy and IHD cohorts. The four pathological scenarios are (a) Healthy heart anatomies + normal myocardial conduction; (b) Healthy heart anatomies + slow myocardial conduction; (c) IHD heart anatomies + normal myocardial conduction; (d) IHD heart anatomies + slow myocardial conduction. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.

Subgroup analysis on IHD patients who met the current criteria of CRT

To test how our models resemble the patients' real conditions, we selected patients from the IHD cohort who met the Class IA indication for CRT ($LVEF \leq 35\%$ and $QRS \text{ duration} \geq 150 \text{ ms}$) ($n=17$), and assessed whether their simulated QRSds in various scenarios still exceeded the 150 ms threshold, reflecting their realistic pathology. Among the 17 patients, 10 had LBBB morphology on their ECG, while 6 showed a right bundle branch block (RBBB) morphology. As shown in Figure 2, none of their simulated QRSds surpassed 150 ms under normal conduction scenarios, regardless of LBBB or normal activation ($113.2 \pm 13.3 \text{ ms}$ and $90.6 \pm 11.5 \text{ ms}$). Under slow conduction scenarios, QRSds increased with 35% and 88% of cases surpassing the 150 ms threshold (normal activation: $134.9 \pm 24.5 \text{ ms}$ and LBBB activation: $172.2 \pm 20.9 \text{ ms}$). Based on these results from our IHD cohort, we observed most of cases exhibiting $QRSd > 150 \text{ ms}$ are due to the combination of both LBBB with conduction slowing, suggesting that these are the most common pathological substrates in patients meeting the current CRT criteria.

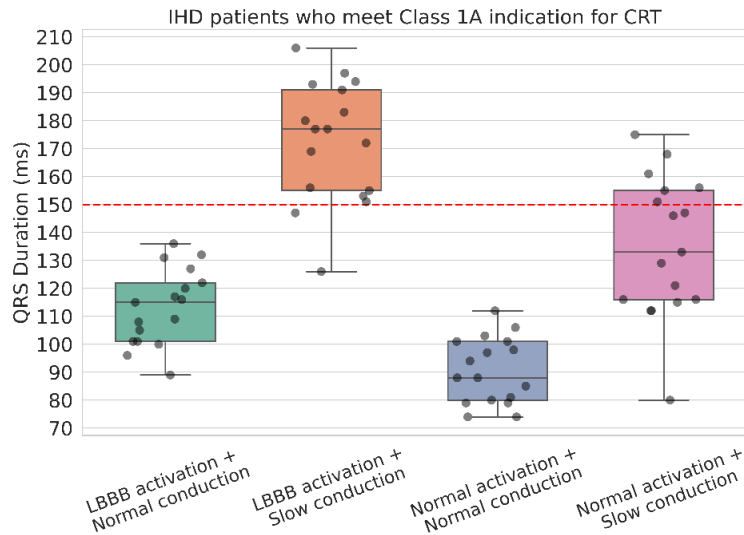


Figure 2: Simulated QRSD in four pathological scenarios for patients who met the Class 1A indication of CRT in the IHD cohort. Four pathological scenarios were included: LBBB or normal activation with normal or slow conduction. Class 1A indication of CRT is defined by LBBB with QRSD $\geq$ 150 ms, LVEF $\leq$ 35% (n=17)

LBBB and non-LBBB Patient stratification using conventional and adjusted QRSD criteria with fixed thresholds

Prior studies suggesting indexed QRSD for improving the identification of female CRT responders often analysed cohorts that already met conventional CRT criteria. However, if these indexed criteria were applied broadly to all heart failure patients, it might identify individuals who do not meet current inclusion criteria for CRT. To evaluate the true predictive accuracy in LBBB patients and ‘false positive’ rates in non-LBBB patients of these QRSD criteria, we apply them to a synthetic model cohort to assess their effectiveness in a general population.

Firstly, the conventional QRSD thresholds (150 ms^{8,9}, 130 ms⁸ and 120 ms⁹) were evaluated for their effectiveness in stratifying male and female patients with and without LBBB. For LBBB patients with slow conduction (Figure 3A, B), the 150 ms threshold identified 71% and 58% of males with IHD and healthy anatomies, respectively, significantly exceeding the 53% and 11% rates for females (both $P<0.03$). Lowering the threshold improved the true positive rate for LBBB females and achieved a non-significant sex difference when using a threshold of 120 ms (IHD: 91% and healthy: 99%), to levels comparable to males (IHD: 96% and healthy: 99%, $P=0.77$ and $P=0.12$). However, the lower thresholds also increased false positive rates among non-LBBB patients with slow conduction (Figure 3C, D), particularly in males (IHD: 76%, healthy: 77%), compared to females (IHD: 57%, healthy: 21%, both $P<0.02$). No significant sex differences were observed in normal conduction scenarios for either LBBB or non-LBBB patients.

Next, the QRSD normalized by heart structural metrics such as LVEDV and LV mass were assessed, using cutoff values: 0.52 and 0.65 ms/mL for LVEDV, and 0.8 ms/g for LV mass, as proposed in previous clinical trials^{4,10,11}. We aimed to test if these indexed QRSD could better identify patients with LBBB, regardless of sex or slow conduction. As shown in Figure 3A, B, indexed QRSD was better at identifying LBBB patients in cases with normal conduction scenarios, where (range: [21.7–99.9%]) of cases met the criteria, compared to conventional QRSD criteria ([0–12.7%]). Among them, LBBB females consistently exhibited better true predictive accuracy than males in normal conduction scenarios ([42.2–99.9%] vs [21.7–95.1%], all $P<0.05$). While the indexed criteria also exhibit greater false positive rates in women (Figure 3C, D), particularly in the normal conduction scenarios ([22.2–

92.6%] vs [7.0-57.2%], all $P < 0.05$). In contrast, in slow conduction scenarios, indexed QRSd criteria lead to both much higher true positive rates for LBBB ([73.2-100%]) and false positive rate for non-LBBB patient selection ([49.7-100%]) with significant sex differences in most cases. Notable exceptions included the 0.52 ms/mL cutoff, which showed no significant sex differences for LBBB patients with healthy or IHD anatomies (healthy and IHD females: 100% and 93.3% vs males: 99.9% and 87.9%, $P = 0.43$ and $P = 0.41$) and the 0.8 ms/g cutoff in LBBB patients with IHD anatomies (female: 93.3% vs 83.8%, $P = 0.1$).

Lastly, we assessed the diagnostic efficacy of indexed QRSd criteria by physical measures such as height using cutoff values of 0.8 and 0.9 ms/cm as proposed previously¹². As shown in Figure 3, both cutoff values demonstrated comparable patient selection rates between sexes across most scenarios, with <10% difference observed in healthy anatomies and slow conduction scenarios using the 0.9 ms/cm ($P < 0.05$). The highest selection rates for LBBB patients occurred in slow conduction scenarios with healthy anatomies (83.7 and 83.9% for females) and IHD anatomies (83.1 and 82.2% for females) using the 0.8 ms/m cutoff. In contrast, the corresponding false positive rates of non-LBBB patients with healthy and IHD anatomies (Healthy: 37.8 and 37.6% for females; IHD: 5.6 and 2.2% for females) are lower, compared to QRSd threshold of 150 ms and all indexed QRSd thresholds by LVEDV and LV mass.

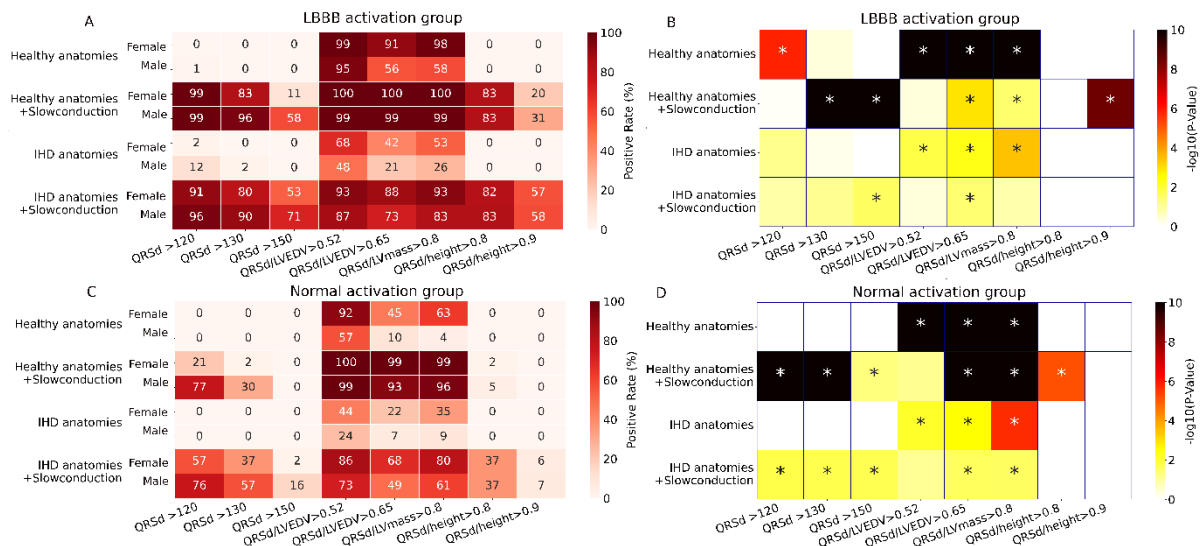


Figure 3: Heatmaps for classification success (positive) rates for LBBB and non-LBBB patients. LBBB (panel a) and non-LBBB Patients (panel c) were classified using conventional and adjusted QRSd criteria by LVEDV, LV mass and height in different sexes for four pathological scenarios including using healthy and IHD heart anatomies with normal and slow conduction. Each cell represents the success (positive) rate in %. Panel b and d represent the corresponding P values of the comparison of the success rate between male and female, for LBBB and non-LBBB activation groups. * $P < 0.05$.

Overall classification performance of conventional and adjusted QRSd criteria across sexes

Prior studies have shown that patients with LBBB generally derive greater benefit from CRT than those without⁶. To distinguish LBBB patients, different criteria based on QRS morphology in the electrocardiograms have been proposed, which lead to significant variability in patient stratification⁷. Here we tested whether QRSd-based criteria can provide a complementary approach to morphology-based assessment, particularly in reducing sex-related bias.

To investigate the classification performance of both conventional and adjusted QRSd criteria in predicting LBBB patients under various pathological scenarios, we have plotted the ROC curves for

each individual QRSd criterion mentioned above and also for both female and male groups to investigate the sex-specific difference (

Figure 4). In general, the AUC for QRSd decreased as the levels of pathological changes increased, for example for the models trained on all cases: healthy anatomies+ normal conduction: 0.985> healthy anatomies + slow conduction: 0.95 > IHD anatomies + normal conduction: 0.886 > IHD anatomies + slow conduction: 0.832, so did for all the other indexed QRSd criteria, no matter of specific sex groups. Overall, the conventional QRSd model consistently outperformed those indexed by LVEDV and LV mass in all scenarios (all $P < 1 \times 10^{-5}$). Interestingly, the model indexed by height demonstrated better performance overall, outperforming indexed LVEDV and LV mass models across all pathological scenarios (all $P < 1 \times 10^{-5}$) while only exceeding QRSd model significantly in two scenarios with healthy anatomies (AUC: normal conduction: 0.994 vs 0.985, $P = 1 \times 10^{-5}$ and slow conduction: 0.972 vs 0.95, $P < 1 \times 10^{-5}$). For the models trained on specific sex groups, the AUCs of conventional QRSd and QRSd indexed by height are similar which both show better predictive power than the QRSd indexed by LVEDV and LV mass.

The optimal thresholds of QRSd increased while the levels of pathological conditions increased, ranging from 87 ms for healthy anatomies + normal conduction to 152 ms for IHD anatomies + slow conduction. Under the IHD anatomies and slow conduction scenario, the optimal threshold of 152 ms for QRSd achieves sensitivity of 0.68 and specificity of 0.87, closely matching the height indexed threshold of 0.86 ms/m with sensitivity of 0.71 and specificity of 0.84. While in the other three scenarios with less remodeling, the height-indexed threshold achieved the best sensitivity and specificity balance, slightly better than QRSd and surpassing QRSd indexed by LVEDV and LV mass.

The male optimal thresholds of QRSd are always larger than the females with differences ranging from 7ms for healthy anatomies+ normal conduction to 13 ms for healthy anatomies + slow conduction. In contrast, the sex-specific differences of optimal thresholds of QRSd indexed by heights are very small (varying by 0.01) under all scenarios, comparing to much larger variations as in QRSd indexed by LVEDV and LV mass (ranges: [0.02, 0.29]).

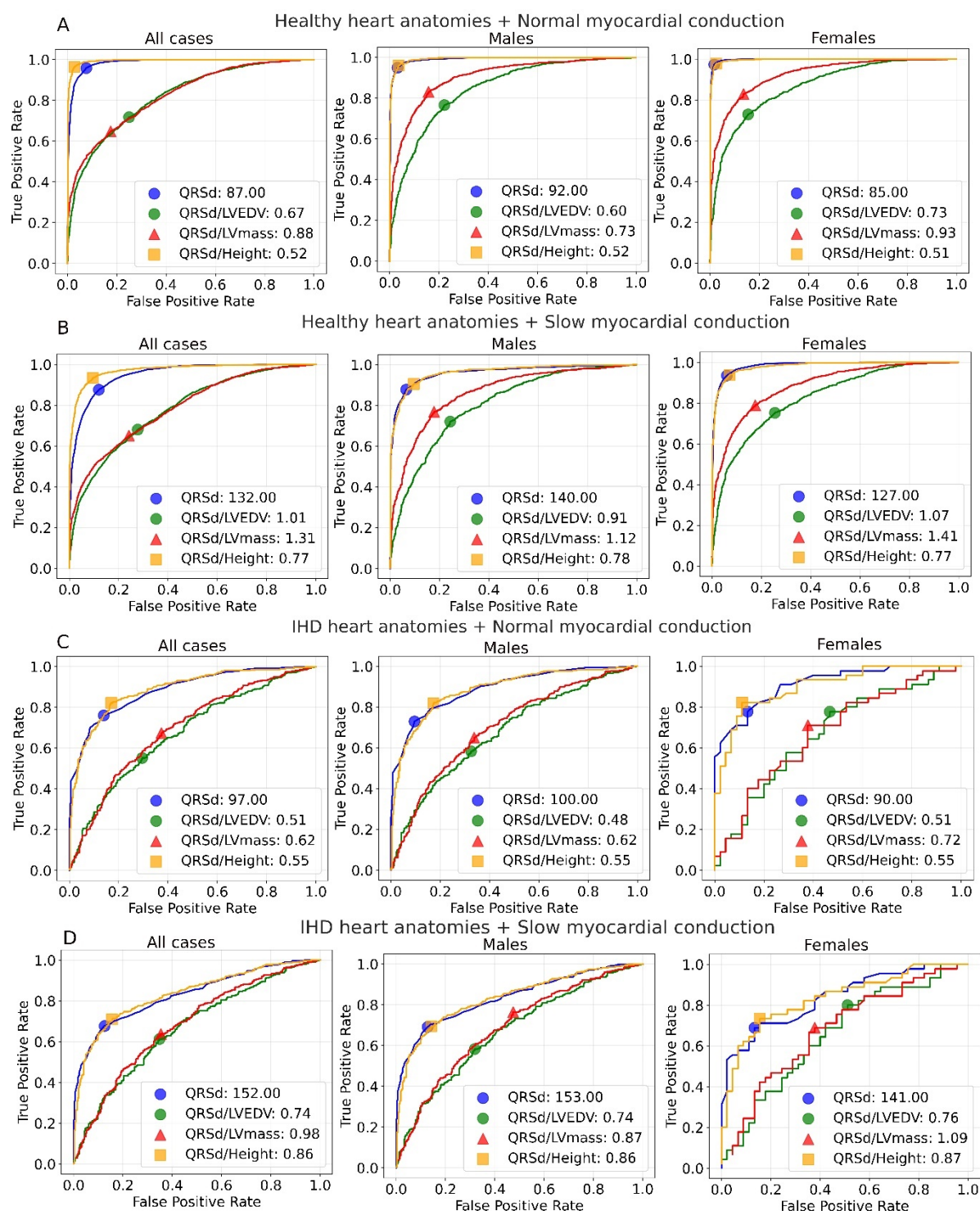


Figure 4: Classification performance of conventional and adjusted QRSd for differentiating LBBB from non-LBBB patients across sex groups and pathological scenarios. QRSd was adjusted by LVEDV, LV mass and height. Performance is shown across four pathological scenarios: (a) Healthy heart anatomies + normal myocardial conduction; (b) Healthy heart anatomies + slow myocardial conduction; (c) IHD heart anatomies + normal myocardial conduction; (d) IHD heart anatomies + slow myocardial conduction. The markers in different shapes represent the optimal threshold for the corresponding predictors.

Clinical Validation in a CRT Cohort

To further evaluate the applicability of the adjusted QRSd criteria in real-world clinical settings, we performed additional simulations in a cohort of patients who had undergone CRT implantation (n =

53), including 12 females (Supplementary Table 1, Supplementary Figure 1). LVEF was comparable between males and females ($26.3 \pm 7.0\%$ vs $27.3 \pm 8.6\%$, $P = 0.63$), as was QRSd (160.0 ± 20.5 ms vs 156.9 ± 13.7 ms, $P = 0.72$). No significant sex differences were observed in LVEDV or RVEDV. However, LV mass was significantly greater in males, being approximately 28% higher than in females (185.7 ± 45.0 g vs 144.6 ± 35.4 g, $P = 0.005$).

We have plotted the ROC curves for all QRSd criteria based on the simulated QRSd to test the classification performance of LBBB scenarios (Figure 5). Similar to the results on healthy and IHD cohorts, the conventional QRSd model consistently outperformed those indexed by LVEDV and LV mass in both normal and slow conduction scenarios (all $P < 0.002$). In contrast, the model indexed by height achieves comparable classification performance as QRSd, outperforming indexed LVEDV and LV mass models across all pathological scenarios (all $P < 0.0002$). Similar to the results on healthy and IHD cohorts, the AUCs of conventional QRSd and QRSd indexed by heights are similar on specific sex groups which both show better predictive power than the QRSd indexed by LVEDV and LV mass. Similar to the healthy and IHD results, the optimal QRSd threshold in slow conduction scenario is longer than in normal conduction scenario (155 ms vs 100 ms). In both scenarios, the height-indexed optimal threshold achieved the best sensitivity and specificity balance, slightly better than QRSd and surpassing QRSd indexed by LVEDV and LV mass. Under the slow conduction scenario, the optimal threshold of 155 ms for QRSd achieves sensitivity of 0.81 and specificity of 0.87, closely matching the height indexed threshold of 0.9 ms/cm with sensitivity of 0.83 and specificity of 0.92. The sex-specific differences of optimal thresholds of QRSd indexed by heights are small (varying by up to 0.07) in both scenarios, comparing to much larger variations as in QRSd indexed by LVEDV and LV mass (varying by up to 0.4).

We further examined simulated 12-lead ECGs of all 12 female CRT cases and 12 age- and BMI-matched male CRT cases to assess whether the simulated ECG waveforms displayed LBBB features described in clinical guidelines (Supplementary Figure 2 and 3). Broad positive QRS complexes without Q waves were observed in the lateral leads across all cases. Dominant negative QRS complexes in V1 were present in most cases, except for four cases (female cases 4 and 6; male cases 7 and 10), while notching or slurring was observed in approximately half of the cases. Reducing myocardial conduction velocity widened the QRS without altering the overall polarity pattern.

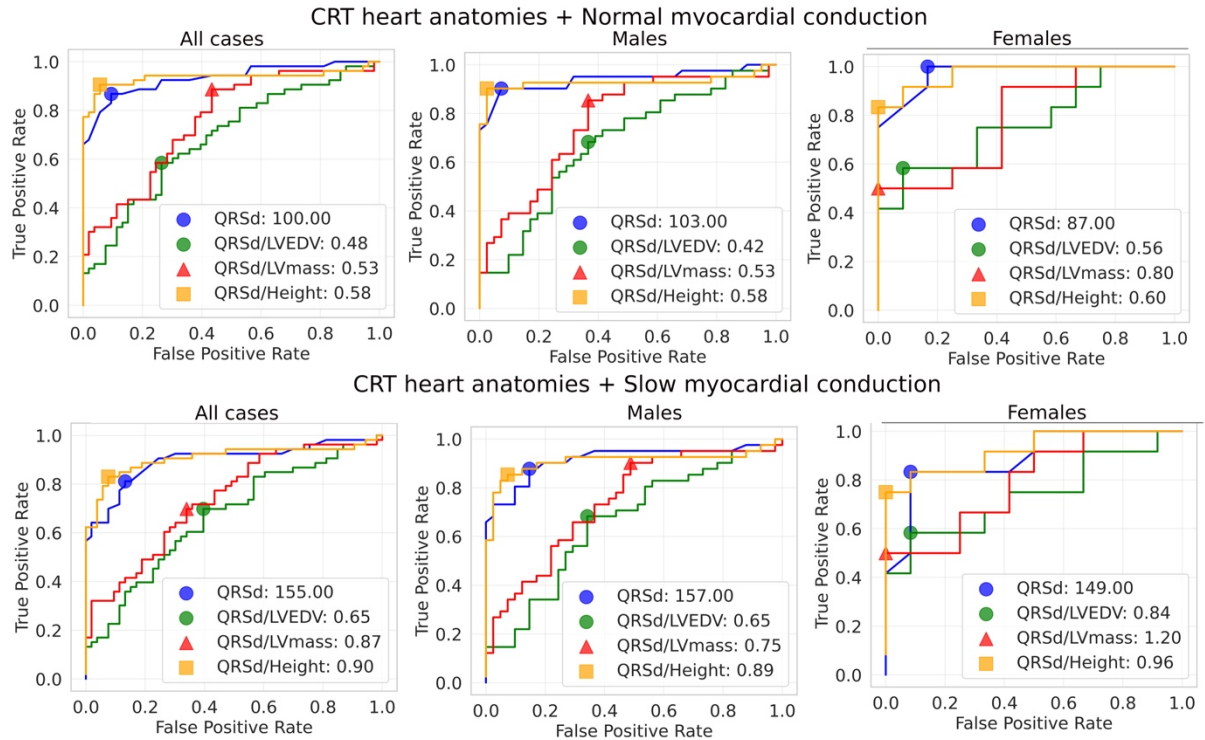


Figure 5: Classification performance assessment of conventional and adjusted QRSd for classifying LBBB patients from non-LBBB patients across sex groups in a CRT cohort. QRSd was adjusted by LVEDV, LV mass, and height. Results are presented for two myocardial conduction conditions: (a) normal myocardial conduction; (b) slow myocardial conduction. Markers of different shapes denote the optimal classification threshold for each predictor.

Discussion

In this large virtual-cohort study, we show that sex differences in QRSd reflect the combined effects of heart size, LBBB activation pattern, and myocardial conduction slowing, and that these factors influence the diagnostic performance of CRT selection criteria. Conventional QRSd thresholds under-select women with modelled LBBB at higher thresholds, whereas indexing by LVEDV or LV mass improves sensitivity at the cost of increased non-LBBB selection. In contrast, height-indexed QRSd largely removes sex disparity while preserving better specificity, suggesting that it merits further evaluation.

Our simulations reproduced key clinical findings^{13,14}, showing baseline simulated QRS durations under normal activation (mean ~78–92 ms) fall within clinically reported normal ranges and reproduce the known sex difference in QRS duration. Added functional remodeling, such as slow myocardial conduction and LBBB dysfunction, only amplified these differences across sexes. The influence of heart size is also evident in our findings: compared with healthy participants, IHD patients had substantially larger hearts and longer baseline QRSd. These results align with previous studies^{15,16} highlighting the role of sex-specific heart sizes and functional remodelling in influencing the QRSd.

To identify the most representative pathological scenarios, we performed a subset analysis on the group of 17 IHD patients who met the Class IA indication for CRT ($LVEF \leq 35\%$ and $QRSd \geq 150$ ms) based on their clinical records. We found that a majority of cases (15 of 17) simulated under the LBBB and slow conduction scenario exceeded the 150 ms threshold, while 6 of 17 cases simulated under LBBB and normal conduction exceeded the 150 ms threshold. These findings suggest that

most patients meeting Class IA criteria are likely to have a combination of LBBB and slowed conduction. Furthermore, our ROC analysis on stratifying LBBB and non-LBBB patients identified an optimal QRSd threshold of 152 ms in IHD patients with slow conduction, closely matching current guidelines and reinforcing the credibility of our approach.

The definition of a ‘true’ LBBB remains debated, and applying ECG criteria in clinical practice can be inconsistent. In our simulations, however, the activation sequence was precisely controlled, ensuring that the modelled LBBB reflected a canonical block pattern. While this provides a clear framework for testing QRSd criteria, extrapolation to real-world patient classification should be further tested and validated.

Our modelling results revealed a significant sex difference in the diagnostic efficacy of conventional QRSd thresholds, consistent with previous studies^{12,16}. The higher 150 ms threshold under-selected LBBB females, whereas the lower 120 ms threshold improved sensitivity for both sexes but increased non-LBBB selection rates, particularly in males. These findings highlight a trade-off between sensitivity and specificity in CRT candidate selection using fixed QRSd thresholds, with distinct implications for male and female patients.

Indexing QRSd by cardiac structural indices such as LVEDV and LV mass partially reduced sex disparities by improving sensitivity for LBBB detection. However, this came at the cost of increased non-LBBB selection and reduced specificity. Persistent sex differences across IHD and CRT cohorts suggest that these structural indices do not fully account for variation in activation patterns and disease-related remodelling.

Height-indexed QRSd demonstrated the most consistent performance across scenarios, reducing sex disparities while maintaining relatively low non-LBBB selection rates. As a stable proxy for baseline heart size, height may better capture anatomical scaling without the confounding effects of disease-related remodelling. However, its clinical utility and optimal thresholds require validation in prospective cohorts.

This can be understood mechanistically, as QRSd depends on the presence of LBBB, conduction speed, and activation path length. While all indexed QRSd metrics account for heart size, height is less likely to be confounded by disease-related remodelling. For example, hypertrophy increases wall thickness and myocardial mass but may have limited impact on activation times, particularly when activation propagates in apical–basal or circumferential directions, as in LBBB. These findings support height-indexed QRSd as complementary to morphology-based assessment, particularly when ECG morphology is ambiguous.

Randomized controlled trials (RCTs) have been instrumental in establishing CRT guidelines, but they have notable challenges in addressing equity and diversity. For example, in the current RCTs, recruited patients are predominantly northern European origin with a female minority (~27%)^{3,12}. Furthermore, discrepancies in the definitions of LBBB morphology between American and European guidelines, as well as across different guideline versions such as ESC-2021 and ESC-2013 have been demonstrated to result in significant variations in patient stratification⁷ and inconsistencies in specificity, particularly in the context of structural remodeling¹⁷. In contrast, our modelling approach offers an unbiased methodology for evaluating CRT patient selection, distinct from the conventional analysis on RCTs, which only included patients meeting the CRT clinical guideline inclusion criteria. This approach enables precise ‘control’ over pathological substrates for each virtual patient, replicating the ‘true LBBB’ condition while integrating known structural and other functional remodelling such as myocardial conduction delay. By creating a comprehensive population-based

library of virtual patients, our method overcomes the biases inherent in retrospective RCT-based analyses and provides a robust in-silico platform for assessing and refining CRT patient selection criteria.

This study provides a novel population-based modelling approach, advanced from previous similar modelling work with a small patient cohort (<10)¹⁷, to evaluate CRT patient selection criteria, free from biases inherent in clinical trial recruitment. Unlike traditional RCTs, our approach simulates controlled pathological scenarios, enabling the assessment of QRSd criteria across diverse patient populations. Importantly, this method captures the full spectrum of LBBB, structural remodelling, and conduction abnormalities, offering a comprehensive framework for refining CRT guidelines.

Our findings carry several translational implications for clinical practice. First, the persistent 7–13 ms sex difference in optimal conventional QRSd thresholds supports prospective evaluation of sex-specific cut-offs; in our simulations, reducing the threshold to 120–130 ms in women substantially reduced sex disparities in LBBB detection, consistent with clinical data showing improved CRT response rates in women at shorter QRSds. Second, a height-indexed QRSd threshold of approximately 0.9 ms/cm achieved near-equivalent classification performance across sexes (optimal sex-specific thresholds varying by <0.07 ms/cm), suggesting that height indexing may be a practical candidate single-threshold approach for future evaluation in sex-equitable patient selection. Third, height-indexed QRSd is best viewed as complementary to ECG morphology criteria, particularly valuable in borderline cases or when morphological assessment is equivocal. We stress that these suggestions are hypothesis-generating and require validation in prospective studies with CRT outcome data before informing guideline revisions.

Several study considerations should be acknowledged. First, the cohorts analysed here are modest in size and enriched for ischemic heart diseases, which differs from typical CRT trial populations where the prevalence of ischemic etiology can be closer to $\sim 30\%$. Furthermore, the healthy and IHD cohorts have mid-range LVEF (mean LVEF ~ 45 – 57%), which differ from the severely reduced LVEF ($<35\%$) required for Class IA CRT indication. The additional analysis in the CRT cohort ($n = 53$; mean LVEF $\sim 27\%$) demonstrates that height-indexed QRSd performs comparably in this clinically representative population; however, the limited sample size warrants cautious interpretation and prospective validation in larger and more representative clinical cohorts.

Second, note that the ‘slow conduction’ scenarios were implemented as a generic representation of impaired propagation, combining ionic remodelling, gap junction uncoupling, and/or fibrotic effects. We did not consider fibrosis or scar of a specific etiology (ischemic or non-ischemic) which, while impacting response to CRT particularly if located at the pacing site, has been shown to have limited effect on QRSd¹⁸. Our findings therefore illustrate mechanistic effects of conduction slowing rather than substrate-specific predictions.

Third, beyond indexed or sex-specific QRS indications for CRT, there is an argument to consider if the LVEF criteria for CRT should also be sex-specific. Currently both men and women require an LVEF $<35\%$. Women have a greater baseline ejection fraction by 1–3%^{19,20}, as seen in our control and IHD cases (Table 1). However, LVEF is routinely measured by echocardiogram in CRT and conducting a randomized study to test whether CRT in women with LVEF <36 – 38% yields improved outcomes compared to an LVEF $<35\%$ would be challenging. Female CRT patients also have lower scar burden than men^{21,22}, which may also contribute to their better outcomes²³. Beela et al²². found a higher CRT response in women was largely explained by their lower prevalence of ischemic cardiomyopathy and smaller extent of myocardial scarring. After correcting for these baseline differences, sex itself was not an independent predictor of CRT response or survival. However, if we consider non-ischemic

LBBB women with shorter (<150 ms) QRS they respond better than men¹⁶. These differences in scar burden and conduction suggest that broader sex-specific evaluation of CRT eligibility criteria may warrant future study.

Fourth, a further concern is about the replication of precordial lead morphology in the simulated ECGs. While all cases exhibited key canonical LBBB features, including a broad QRS (100%), QS or rS V1 (83%), QS or rS V2 (25%) and notching or slurring in >1 V1,2,5,6 (100%), a subset of cases demonstrated a dominant R wave in V2-V3. This is likely attributable to uncertainty in the placement and orientation of the patient-specific heart model within the representative torso. In studies of postural changes²⁴ in heart position is known to influence R wave amplitude by up to 50%. To test this, we performed a sensitivity analysis, in which the heart was displaced 2 cm in each direction along axes derived from subject-specific limb lead positions. This confirmed that R wave amplitude in leads V1-V5 is highly dependent on heart position (Supplementary Figures 5-8). Importantly, QRSD in this study was derived from the vectorcardiogram (VCG) from the ECGs, rather than individual lead ECGs, which renders it substantially less sensitive to heart position. Quantification of this effect in the CRT dataset yielded mean QRSD differences of -1.36 ± 3.17 ms (right), 0.81 ± 3.69 ms (left), -5.51 ± 11.05 ms (up), and 1.19 ± 6.74 ms (down) (Supplementary Figures 4), confirming that positional uncertainty has only a minor influence on the primary metric reported in this study.

Overall, our findings reveal substantial sex differences in QRSD and the diagnostic efficacy of conventional thresholds. While indexing QRSD by cardiac structural metrics such as LVEDV and LV mass improved sensitivity, it also reduced specificity and failed to eliminate sex disparities. In contrast, height-indexed criteria effectively resolved these differences while maintaining diagnostic accuracy, supporting further evaluation of height-indexed QRSD as a complementary biomarker for CRT candidate selection. These findings highlight a mechanistic basis for sex differences in LBBB detection, which may influence CRT outcomes, and the importance of incorporating sex-specific factors in future studies evaluating CRT selection criteria.

Methods

Study population and mesh generation

This study consists of a cohort of healthy participants and a clinical cohort of IHD patients. The healthy cohort is collected from the UK biobank (UKBB) (<https://www.ukbiobank.ac.uk/>), a large-scale prospective study of middle/old age individuals in the UK initiated in 2006, to enable better understandings in the determinants of health and disease in the general UK population. The UK Biobank study was approved by the North West - Haydock Research Ethics Committee (REC reference: 21/NW/0157). All UK Biobank participants provided written informed consent prior to enrolment. From an initial cohort of 3461 participants⁵, 2627 participants with no cardiovascular disease (CVD) were included in this study. Participants with any diagnosis of 'Diseases of the Circulatory system' (I00-I99) according to the International Classification of Diseases- 10th Edition (ICD-10) (Data-Field 41270) were excluded. The clinical cohort of patients with IHD (n=359), was recruited at the Royal Brompton & Harefield NHS hospital as previously reported²⁵. The IHD study was approved from the National Research Ethics Service under the Cardiovascular Magnetic Resonance for the Assessment of Myocardial Fibrosis Using Delayed Contrast Hyperenhancement study (reference 07/H0708/83; approved 27 March 2008) and the Cardiovascular Biomedical Research Unit Biobank (reference 09/H0504/104+5; approved 3 July 2014). Written informed consent was obtained from all participants prior to inclusion in the study. LBBB morphology in IHD patients was identified from clinical ECG records using European Society of Cardiology (ESC) 2013

CRT guideline: QRS duration ≥ 120 ms, QS or rS in lead V1, broad notched or slurred R wave in the lateral leads (I, aVL, V5–V6), absence of Q waves in leads V5 and V6.

The cardiac magnetic resonance (CMR) dataset of the CRT cohort was derived from a prospective cohort study conducted at the University of Virginia evaluating imaging predictors of response to CRT²⁶. The study was approved by the Institutional Review Board for Human Subjects Research at the University of Virginia (UVA IRB-HSR protocols 18641 and 19808), in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. Patients with chronic systolic heart failure (left ventricular ejection fraction $\leq 35\%$) and a guideline-based indication for CRT underwent comprehensive pre-implantation CMR, followed by repeat imaging approximately 6 months after device implantation. Imaging was performed on a 1.5-T scanner and included cine steady-state free precession (SSFP) and gradient echo sequences for ventricular volumes and function, displacement encoding with stimulated echoes (DENSE) for myocardial strain and dyssynchrony assessment (including CURE-SVD), and late gadolinium enhancement (LGE) for scar characterization, along with 12 lead ECGs. The pre-CRT scans were included in the study. Quantitative analyses were performed using standardized, semi-automated methods in a blinded core laboratory, yielding measures of ventricular volumes, ejection fraction, strain-based dyssynchrony, and myocardial scar burden.

Patient-specific biventricular meshes were generated from CMR images for the three cohorts as described previously⁵. In brief, the CMR images taken at the end-diastolic phase were automatically segmented to derive contours and landmarks of both ventricles. They were then processed using an established atlas-based pipeline to generate surface meshes, which were subsequently converted to volumetric meshes.

To enable consistency in simulation setups, we implemented a morphological coordinate system, also known as universal ventricular coordinates (UVCs), for describing positions within ventricles based on the apical-basal (Z), transmural (ρ) (from endocardium to epicardium), rotational (φ) (anterior, anteroseptal, inferior, inferolateral, anterolateral) and chamber-wise (left ventricle and right ventricle) coordinates, and applied to all models. Biventricular myocardial fibre structure was incorporated using a rule-based method with transmural angle ranging from 60° to -60° longitudinally and -65° to 25° transversely, transitioning from endocardium to epicardium. Details regarding population sample selection and mesh quality control have been described previously⁵.

Electrophysiological (EP) simulations

The electrophysiological simulations were performed using the cardiac arrhythmia research package (CARP)²⁷. A Reaction-Eikonal model without diffusion was used to compute the ventricular activation times and transmembrane potential dynamics²⁸. Similar to previous studies^{5,29}, the ventricular depolarization during sinus rhythm was initiated using a fascicular-based model to replicate the His-Purkinje activation. Specifically, as shown in Figure 6, there are five early activation sites located as follows: three in the left ventricle (LV)-anterior (af), septal (sf) and posterior(pf) walls, and two in the right ventricle (RV)-septal wall (sf) and the lateral moderator band (mod). Early activation sites are represented as endocardial disks with thickness as 5% of ventricular wall ($\rho = 0.05$) and the radius as $Z=0.05$. A sub-endocardial (SE) layer with faster conduction was implemented as a thin layer near the endocardium, defined by transmural coordinates ρ_{SE} and apical-basal coordinates $Z_{min,SE}, Z_{max,SE}$. All parameters mentioned above are shown in Table 2, and their values were set as the median values derived from previous measurements reported in the literature.

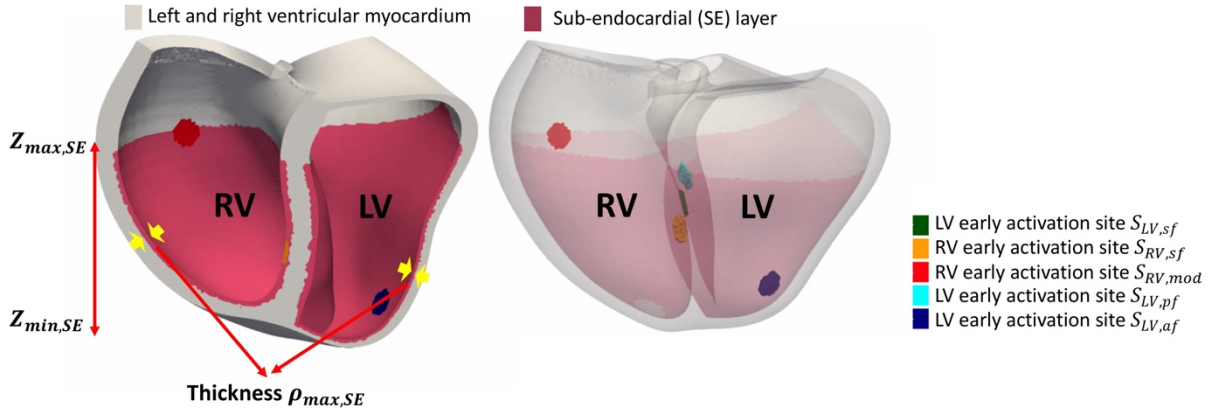


Figure 6: The fascicular-based model replicates the realistic ventricular activation modulating by the His-Purkinje system.

Parameters	Value	Description	References
$Z_{LV,sf}$	0.5	Apical-basal coordinate for LV septal fascicle	30–33
$Z_{LV,pf}$	0.5	Apical-basal coordinate for LV posterior fascicle	30–32
$Z_{LV,af}$	0.7	Apical-basal coordinate for LV anterior fascicle	30–32
$Z_{RV,sf}$	0.6	Apical-basal coordinate for RV septal fascicle	30–32
$Z_{RV,mod}$	0.4	Apical-basal coordinate for RV moderate band fascicle	30–32
$\phi_{LV,sf}$	0	Rotational coordinate for LV septal fascicle	30–33
$\phi_{LV,pf}$	-1	Rotational coordinate for LV posterior fascicle	30–33
$\phi_{LV,af}$	2.37	Rotational coordinate for LV anterior fascicle	30–33
$\phi_{RV,sf}$	1	Rotational coordinate for RV septal fascicle	30–33
$\phi_{RV,mod}$	0	Rotational coordinate for RV moderate band fascicle	30–33
$t_{LV,sf}$	15	Firing time for LV posterior fascicle	30
$t_{LV,pf}$	15	Firing time for LV anterior fascicle	30
$t_{LV,af}$	15	Firing time for RV septal fascicle	30
$t_{RV,sf}$	15	Firing time for RV moderate band fascicle	30
$t_{RV,mod}$	15	Firing time for LV posterior fascicle	30
ρ_{SE}	0.155	Transmural coordinate for SE layer	29
$Z_{min,SE}$	0.08	The minimum apical-basal coordinate for SE layer	33
$Z_{max,SE}$	0.75	The maximum apical-basal coordinate for SE layer	33–35
$R_{myo,SE}$	5	The ratio of conduction velocity (CV) in SE layer to CV in myocardium	29,36,37

Table 2: The electrophysiological parameters used for defining the fascicular-based model.

Myocardium was simulated as a transversely isotropic medium with a conduction velocity of 0.65 m/s along fiber directions and an anisotropy ratio of 0.42 for the transverse fiber direction³⁸. Normal sinus rhythm activation was simulated by stimulating all five early activation sites, while the LBBB activation was simulated by stimulating only two RV sites, as shown in Figure 7. Given that the torso information is unavailable, the heart models were registered to a heart enclosed in an existing torso model³⁹ using the UVCs. Within this reference torso, the locations of electrodes used in measuring 12-lead ECGs were identified, the corresponding extracellular potentials were simulated using *Phi_e* recovery method⁴⁰ and the ECGs were computed. The QRSd was computed by finding the time points at which the spatial velocity exceeds 0.15 of the maximum spatial velocity in the reconstructed corresponding vectorcardiogram (VCG) from 12-lead ECGs, which fuse the information in ECG traces³⁹.

Slowed cardiac conduction, representing pathological processes such as ionic remodeling, gap junction uncoupling, and fibrosis following ischemia⁴¹, was simulated by reducing the model conduction velocity along fiber direction to 0.4 m/s, based on previous experimental and modelling studies^{42,43}, while the conduction velocity for the transverse fiber direction along with conduction velocity in the sub-endo layer were scaled accordingly using the ratios mentioned above. For each patient-specific anatomical model, four scenarios were simulated: (1) normal activation with normal conduction, (2) normal activation with slowed conduction, (3) LBBB activation with normal conduction, and (4) LBBB activation with slowed conduction.

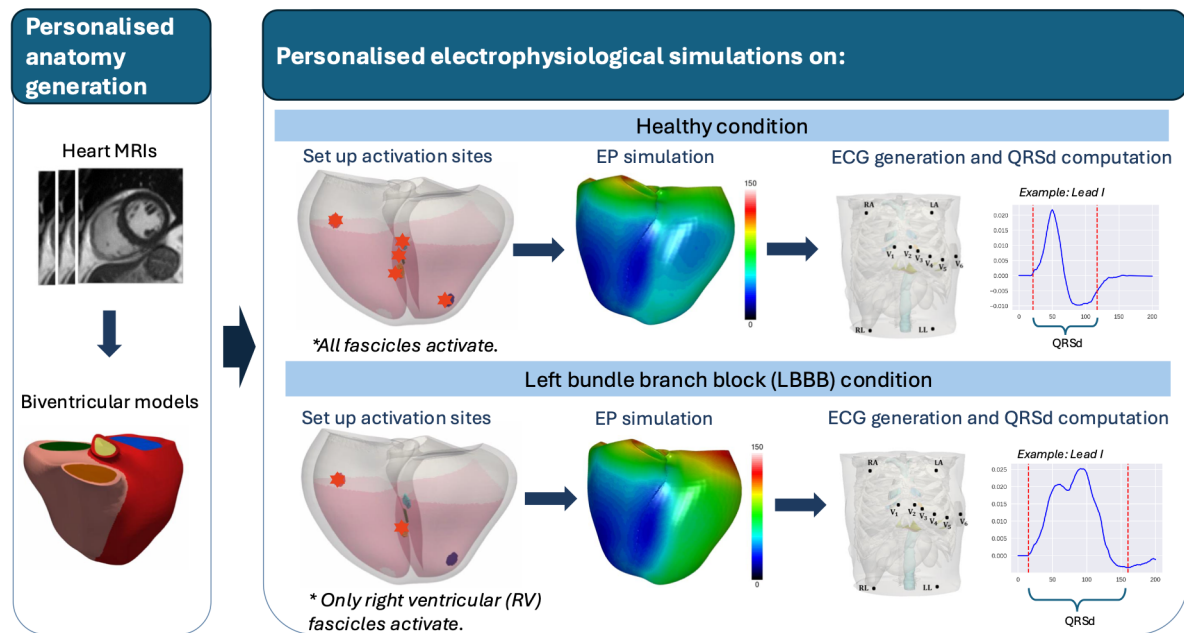


Figure 7: Overview of the workflow of the in-silico trial for LBBB. This workflow has the following steps. (1) patient-specific biventricular mesh construction from CMR images; (2) electrophysiological simulation using the fascicular-based activation model; (3) ECG computation via the lead field recovery method using the reference torso electrode positions; and (4) QRSd extraction from ECGs.

Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviation and compared using the Mann-Whitney U-test, a non-parametric statistical test, due to the non-normal data distribution. Categorical variables are presented as percentages and compared using the Chi-square test or Fisher exact test, as appropriate. The receiver operating characteristic (ROC) curves were generated for all conventional and indexed QRSd criteria across simulated scenarios. Optimal thresholds were determined using Youden's J statistics. The Delong test was used to compare the area under the receiver operating characteristic (AUC) of any pairs of correlated predictors.

Data availability

This study has three datasets: the UKBB cohort, the IHD cohort and the CRT cohort. For the UKBB cohort, the imaging data and non-imaging participant phenotypes are available from the UK Biobank via a standard application procedure at <http://www.ukbiobank.ac.uk/register-apply>. The data for the IHD and CRT cohort are not publicly available due to patient privacy and the absence of consent for public access. It can be accessed through reasonable request for an institutional data-sharing agreement.

Code availability

The anatomical model generation pipeline is available at <https://www.github.com/cdttk/biv-volumetric-meshing>, which includes the use of open simulator: openCARP, available at <https://opencarp.org/>. The electrophysiological simulations were performed using the Reaction-Eikonal model, which is part of a proprietary version of the Cardiac Arrhythmia Research Package (CARP)⁴⁴ and requires a license. However, the reaction-eikonal simulations can also be performed in openCARP (opencarp.org).

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Author contributions

S.Q., C.R., A.Y., P.L., M.B. and S.N. conceived and designed the study. S.Q., D.U., and E.F. constructed anatomical models for the UK biobank cohort. R.E.J., H.Z., S.P., B.P.H. and D.H. contributed to the data collection and quality control check of the clinical cohort of patients with ischemic heart disease, and S.Q., H.Z., A.Y. and M.B. contributed to the model construction of those patients. G.P. and E.V. contributed to the development and maintenance of the CARPEntry software used for electrophysiological simulations. D.B. and K.C.B. contributed to the data collection and quality control check of the CRT cohort, and C.R., D.U., and A.Q. contributed to the model construction of those patients. S.Q. performed the electrophysiological simulations for LBBB/non-LBBB scenarios on three cohorts, analyzed the results and wrote the manuscript. All authors contributed to the manuscript revision and approved the final submitted version.

Competing Interests

The authors declare no competing interests.

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Figure legends

Figure 1: Comparison of QRSd simulated in four pathological scenarios of both sexes in both healthy and IHD cohorts. Four pathological scenarios are (a) Healthy heart anatomies + normal myocardial

conduction; (b) Healthy heart anatomies + slow myocardial conduction; (c) IHD heart anatomies + normal myocardial conduction; (d) IHD heart anatomies + slow myocardial conduction. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

Figure 2: Simulated QRSd in four pathological scenarios for patients who met the Class IA indication of CRT in the IHD cohort. Four pathological scenarios were included: LBBB or normal activation with normal or slow conduction. Class IA indication of CRT is defined by LBBB with $\text{QRSd} \geq 150$ ms, $\text{LVEF} \leq 35\%$ ($n=17$)

Figure 3: Heatmaps for classification success (positive) rates for LBBB and non-LBBB patients. LBBB (panel a) and non-LBBB Patients (panel c) were classified using conventional and adjusted QRSd criteria by LVEDV, LV mass and height in different sexes for four pathological scenarios including using healthy and IHD heart anatomies with normal and slow conduction. Each cell represents the success (positive) rate in %. Panel b and d represent the corresponding P values of the comparison of the success rate between male and female, for LBBB and non-LBBB activation groups. * $P < 0.05$.

Figure 4: Classification performance of conventional and adjusted QRSd for differentiating LBBB from non-LBBB patients across sex groups and pathological scenarios. QRSd was adjusted by LVEDV, LV mass and height. Performance is shown across four pathological scenarios: (a) Healthy heart anatomies + normal myocardial conduction; (b) Healthy heart anatomies + slow myocardial conduction; (c) IHD heart anatomies + normal myocardial conduction; (d) IHD heart anatomies + slow myocardial conduction. The markers in different shapes represent the optimal threshold for the corresponding predictors.

Figure 5: Classification performance assessment of conventional and adjusted QRSd for classifying LBBB patients from non-LBBB patients across sex groups in a CRT cohort. QRSd was adjusted by LVEDV, LV mass, and height. Results are presented for two myocardial conduction conditions: (a) normal myocardial conduction; (b) slow myocardial conduction. Markers of different shapes denote the optimal classification threshold for each predictor.

Figure 6: The fascicular-based model replicates the realistic ventricular activation modulating by the His-Purkinje system. Reproduced by kind permission of UK Biobank©.

Figure 7: Overview of the workflow of the in-silico trial for LBBB. This workflow has the following steps. (1) patient-specific biventricular mesh construction from CMR images; (2) electrophysiological simulation using the fascicular-based activation model; (3) ECG computation via the lead field recovery method using the reference torso electrode positions; and (4) QRSd extraction from ECGs. Reproduced by kind permission of UK Biobank©.