Cardiovascular outcomes in patients with intraventricular conduction blocks: A sixteen-year follow-up in a state-wide database

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Heart failure;
Mitral regurgitation;
Atrial fibrillation

Abstract
Background: To assess the adverse clinical effects of left anterior hemiblock alone or in combination with right bundle branch block and of complete left bundle branch block in comparison with isolated right bundle branch block and the relationship of these effects with altered mechanoelectric factors resulting in left ventricular dysfunction.

Methods: In a 16-year follow-up study using a statewide database, we studied the occurrence of mortal and morbid cardiovascular (CV) events among patients without apparent ischemic heart disease who had left anterior hemiblock (LAHB, n = 4273), right bundle branch block (RBBB) with LAHB (BFBB, n = 1857) and left bundle branch block (LBBB, n = 9484 compared to isolated RBBB (n = 25288).

Results: After adjustment for demographics, co-morbidities and insurance, LAHB was associated with a significant excess risk of all-cause death (HR 1.134, 95% CI 1.061-1.213, p < 0.0001) and CV death (HR 1.329, 95% CI 1.174-1.501, p < 0.0001). BFBB was associated with excess HF (HR 1.190, 95% CI 1.048-1.351, p < 0.0071), all-cause death (HR 1.440, 95% CI 1.045-1.252, p = 0.0036) and CV death (HR 1.210, 95% CI 1.020-1.436, p < 0.0001). LBBB was associated with an excess risk of MR (HR 1.307, 95% CI 1.116-1.530, p < 0.0009), HF 1.177, 95% CI 1.097-1.263, p < 0.0001) and CV death (HR 1.220, 95% CI 1.106-1.345, p < 0.0001).

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Conclusions: In patients without apparent ischemic heart disease, the presence of LAHB alone or in combination with RBBB imparts increased risk of CV and all-cause death compared to isolated RBBB. BFBB is also associated with an increased risk of HF.

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1. Introduction

Intraventricular conduction blocks (ICBs) are associated with adverse cardiovascular outcomes in studies of ischemic and non-ischemic cardiomyopathy. Left bundle branch block (LBBB) is consistently associated with higher risk compared to isolated right bundle branch block (RBBB). A suggested explanation for these adverse outcomes has been that ICBs are associated with inter and/or intraventricular dyssynchrony and specific regional contraction abnormalities of the ventricles. It has been proposed that the presence of left anterior hemiblock (LAHB) alone or in combination with RBBB is associated with delayed depolarization of the posterobasal/lateral segments of the left ventricle (LV), leading to adverse consequences in overall left ventricular function and possibly mitral valve competency. Considerable controversy exists regarding specific contraction abnormalities associated with ICBs, their importance in placing the left ventricular lead during cardiac resynchronization therapy (CRT) and on the effect of ICBs on long term clinical outcomes.

In a statewide database with up to 16 year follow-up (average 5.8 years), we investigated whether LAHB in isolation or with RBBB (BFBB), is a discrete marker of higher risk compared to isolated RBBB, by examining the occurrence of mortal and morbid events among 41,024 patients without clinical evidence of ischemic heart disease (IHD).

2. Methods

2.1. Data Sources

We used data from the Myocardial Infarction Data Acquisition System (MIDAS) database for this study. MIDAS includes the hospital discharge records of patients with myocardial infarction and invasive cardiovascular procedures who were admitted to New Jersey (NJ) non-federal acute care hospitals since 1986. It contains abstracted discharge data, including the primary reason for admission and up to eight additional diagnoses, derived from the NJ statewide hospital uniform billing system. Starting in 1994, the database was made more comprehensive by including all admissions of patients with any cardiovascular diagnosis with or without a myocardial infarction.

On an annual basis, MIDAS data were merged with the NJ Death Registration Files to obtain death information (date and cause of death), including out-of-hospital deaths. Matching was performed using the Link King, a record linkage and consolidation software that integrates a deterministic algorithm with a probabilistic algorithm. The algorithm was found to have a sensitivity of 79% and positive predictive value of 99%.

To obtain an estimate of deaths occurring outside the state of NJ, 7308 randomly selected MIDAS records from the years 1986 to 2004 were matched to the National Death Index. Only 14 deaths (0.19% of the sample) occurred out-of-state within 30 days of discharge and 119 (1.63%) occurred within 1 year of discharge. Deaths occurring in hospice or home hospice were included in the in-hospital deaths.

Entering the data is the responsibility of the individual hospitals. However, state and federal authorities audit the completeness and accuracy of the data. This database was previously audited using a random sample of charts to verify the accuracy of the information.

NJ residents hospitalized outside the state of NJ are not included in this analysis. While this introduces some error, the number is probably small.

2.2. Study Patients

We examined the discharge records of 4,407,455 patients and identified 51,408 patients with a first admission with a diagnosis of ICB. Among these patients with ICBs, 10,384 were admitted with a diagnosis of IHD during the follow-up period and were excluded. The remaining 41,024 patients are the subjects of the current study. They were admitted to New Jersey hospitals between 1994 and 2013 with a first admission with a diagnosis of ICB and were over the age of 20 years. Patients with an index diagnosis of ischemic heart disease prior to the index admission for ICB were excluded. Each patient was followed up to December 31, 2013 or intervening death. Isolated RBBB was chosen as the control group as early LV depolarization is entirely normal.

2.2.1. Study Variables

The ICBs were categorized as RBBB without LAD (ICD9 426.4), LAHB (ICD 462.2), RBBB+LAHB (BFBB; ICD 426.52) and LBBB (ICD 426.3). LBBB was undifferentiated in terms of the presence or absence of LAD. Five separate outcome variables were considered for this study: mitral regurgitation (MR; ICD 424.0), atrial fibrillation (AF; ICD 427.31), heart failure (HF; ICD 428.0 to 428.4), cardiovascular and all-cause mortality. The covariates considered were age, gender, race, health insurance and diagnoses other than ICBs, listed in the abstracted discharge data under data sources, either as the primary diagnosis or as comorbid conditions. These included hypertension (ICD9 401 to 405), chronic pulmonary disease (ICD9 490 to 508), diabetes (ICD9 250), renal disease (ICD9 580 to 589) and cancer (ICD9 140). Patients with a first admission for ICD
were not evaluated for the prior occurrence of MR, atrial fibrillation or CHF.

2.3. Statistical analysis

We compared patient characteristics across ICB categories. Event rates were calculated using Cox proportional hazards regression models. In each Cox model, event rates were compared between each of the study groups (LAHB, RBBB + LAHB, and LBBB) and the control group (RBBB) using hazard ratios with 95% confidence intervals. Kaplan-Meier survival curves for each outcome (MR, AF, HF, all cause death and cardiovascular (CV) death) were plotted over time separately for the three study groups and the control group. The models were adjusted for the covariates listed above, as baseline characteristics differed among groups.

Diagnoses included in the abstracted discharge data, exclusive of the outcomes listed above, were not considered. Statistical analyses were performed with the use of SAS 9.3 software (SAS Institute).

The institutional review boards of the State of New Jersey Department of Health and Senior Services and the UMDNJ-Robert Wood Johnson Medical School approved the study.

3. Results

3.1. Patient Characteristics

The number of patients with RBBB and left posterior hemiblock (122) was very small and had few events (no MR, 9 Afib, 8 HF, 4 CV death and 24 all-cause deaths, all non-significantly different compared to patients with isolated RBBB). LBBB was present in 9,484 patients; LAHB in 4,273, RBBB with LAHB in 1,857 and isolated RBBB in 25,288. The study population primarily consisted of white (80.7%), males (50.5%) who were on average 65 years old (63.7±17.8) and were mostly either on Medicare (44.2%) or a commercial insurance (47.3%). They were followed for up to 16 years with an average follow-up time of 5.8 years. Most of this population had co-morbid conditions, such as hypertension (52.7%), chronic obstructive pulmonary disease (14.9%), diabetes (15.3%), cancer (10.2%) and chronic renal disease (4.6%) (Table 1).

Patients with RBBB + LAHB and those with isolated RBBB were predominantly male (58.4% and 56.2%, respectively). Those with LBBB were mostly female (66.9%). However, there was no gender difference among those with LAHB (51.5% male).

3.1.1. Outcomes

The following five outcomes were evaluated: MR, AF, HF, cardiovascular and all-cause mortality. The Kaplan-Meier Curves show that those with RBBB + LAHB had lower survival rates for HF, cardiovascular or all-cause mortality. Patients with LBBB had the lowest event-free rates in regard to MR, HF and CV death. LAHB patients had lower survival rates for cardiovascular and all cause death (Figures 1 and 2).

Table 2 shows the adjusted hazard ratios for MR, AF, HF, cardiovascular and all-cause mortality. Compared to isolated RBBB patients, MR occurred more frequently among patients with LBBB (HR 1.307, 95% CI: 1.116-1.530, \( p < 0.0009 \)). Regarding AF, none of the study groups were associated with a significant excess risk. The risk of heart failure was significantly higher in two groups (RBBB + LAHB: HR 1.19 95% CI: 1.048-1.351, \( p = 0.0071 \) and LBBB: HR 1.177 95% CI: 1.038-1.326, \( p = 0.0079 \)).

### Table 1 Baseline Characteristics Stratified by BBB.

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<th></th>
<th>LAHB</th>
<th>RBBB</th>
<th>LBBB</th>
<th>RBBB</th>
<th>RB + LP</th>
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<tr>
<td>Total</td>
<td>4,273</td>
<td>25,288</td>
<td>9,484</td>
<td>1,857</td>
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<td>Male</td>
<td>2,202</td>
<td>14,219</td>
<td>3,143</td>
<td>1,085</td>
<td>20,719</td>
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<td>Female</td>
<td>2,011</td>
<td>11,073</td>
<td>6,341</td>
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<td>White</td>
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<td>20,048</td>
<td>7,885</td>
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<td>740</td>
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<td>859</td>
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<tr>
<td>Commercial</td>
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<td>12,357</td>
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<tr>
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<td>Renal</td>
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<td>435</td>
<td>45</td>
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<td>681</td>
<td>3,843</td>
<td>1,245</td>
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<td>6,094</td>
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<tr>
<td>Age Mean ± SD</td>
<td>67.4±15.9</td>
<td>68.3±15.7</td>
<td>60.8±18.4</td>
<td>61.5±16.8</td>
<td>63.7±17.8</td>
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<tr>
<td>Survival Time</td>
<td>5.9±5.6</td>
<td>5.8±5.2</td>
<td>5.2±4.8</td>
<td>5.8±5.3</td>
<td>5.4±5.0</td>
</tr>
</tbody>
</table>

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95% CI: 1.097-1.263, \( p < 0.0001 \). Cardiovascular death was higher in the LAHB (HR 1.329 95% CI: 1.174-1.505, \( p < 0.0001 \)); RBBB+LAHB (HR 1.210 95% CI: 1.020-1.436) and LBBB (HR 1.220 95% CI: 1.106-1.345, \( p < 0.0001 \) for both) groups. For all-cause death, excess risk was identified for the LAHB (HR 1.134 95% CI: 1.061-1.213, \( p = 0.0002 \)) and (RBBB+LAHB: HR 1.44 95% CI: 1.045-1.252, \( p = 0.0036 \)) groups.

In summary, in this study of patients without admission for ischemic heart disease, patients with LAHB, BFBB (RBBB + LAD) and LBBB (undifferentiated as to frontal axis) had worse outcomes compared to patients with isolated RBBB.

4. Discussion

Considerable uncertainty exists regarding the clinical significance of isolated LAHB, with one study in 2007 stating that isolated LAHB does not itself imply a risk factor of cardiac morbidity or mortality, and in a healthy population, it must be regarded as an incidental electrocardiographic finding, which is not the case in hospital populations. Additionally, ICBs have been associated with increased morbidity and mortality in long-term follow-up studies of individuals with initially apparently normal cardiac function.7,11,20,21 While LBBB has been associated with the most adverse outcomes, in a study that identified the frontal QRS axis,7 LBBB with LAD was associated with even more adverse outcomes. In the same study, RBBB was found to be associated with similar adverse outcomes as LBBB without LAD. In a recent analysis of the risk of incident HF in the ARIC study, it was concluded that "VCDs except for isolated RBBB are strong predictors of incident HF, and HF risk is further increased as the QRS duration is prolonged >140 ms."6 The prevalence of LAHB in the normal population varies from 0.9% to 6.2%. In our study of a hospital-based population, the overall prevalence was 10.6%, while the prevalence among the non-ischemic group was 10.4%. ICBs are considered to be due to abnormalities of the His Purkinje System (HPS), its distribution and transmission velocities. The ventricular conduction system comprises the main bundle, RBBB, LBBB and the subendocardial peripheral conduction system, thought to develop from the trabecular ventricular component. Studies in embryology indicate that, before the onset of overt chamber formation, an ECG can be recorded. In the early embryonic heart (stage HH14), no specialized/distinct cells of a conduction system can be recognized.7

4.1. Myocardial Structure and Function

The ventricular myocardial band (VMB), a concept developed over the last 50 years, has led to an explanation of the way the heart performs its double function, ejection and suction of blood. Diffusion-tension MRI studies on intact human beating hearts have confirmed that myocardial fibers within the ventricular mass are arranged in layers of counter-wound helices, encircling the ventricular cavities. Patterns of contractile activities within the ventricular myocardium may or may not precisely correspond with patterns of electrical excitation. The apical loop of the VMB is the principal motor of the heart. The ventricles have the ability to translate 15% linear sarcomere shortening into an ejection fraction of greater than 50% and wall thickening greater than 30%.5,9
Figure 2  Survival Curves for mitral regurgitation, atrial fibrillation, heart failure and cardiovascular death by type of intraventricular conduction block. Kaplan-Meier survival curves (from top to bottom) for mitral regurgitation, atrial fibrillation, heart failure and cardiovascular death by type of intraventricular conduction block. Red denotes LAHB; blue denotes RBBB+LAHB; black denotes LBBB; green denotes RBBB.
The most important part of ventricular diastole (i.e., the rapid filling phase), during which it receives more than 70% of the stroke volume, belongs to the active muscular contraction of the ascending segment of the apical band.

It is widely accepted that electrical coupling between myocardial cells is accomplished by cell-to-cell transmission via the gap junctions.

### 4.2. Prior Observations

Carl Wiggers, in his monograph published in 1928 (chapter 8), discussed "the fractionate nature of ventricular contraction". He stated that the initial concave rise in LV pressure may be accounted for by the continued entry of new fractionate contractions. This early phase of isometric contraction, averaging 0.038 sec, he designated "the entrant phase". Changes in the gradient and amplitude of the total muscular contraction of a cardiac chamber are caused either by variation of the number of fractions excited or by alterations of the state of reactivity. He concluded that fractionate contractions continue after the point arbitrarily adopted (the incisura) as a criterion of the end of mechanical systole. In 1930, Katz demonstrated a drop of intraventricular pressure below 0 during the rapid filling phase, preceded by a large and rapid increase of the ventricular volume capable of producing effective blood suctioning.

The direction, magnitude and spatial distribution of early and late vectors on VCG most likely represent the fractional entry into contraction (regional strain) and the amount of the additive muscle mass involved. These prior observations are consistent with studies on regional strain and the continuing contraction of segments of the LV during the early diastolic period of rapid filling. Post-systolic shortening was reported predominately in the apical and basal segments of the septal, anteroseptal and anterior walls, and its duration of approximately 1/6 of the systolic duration results in a relative increase in strain of 19\(^\frac{6}{10}\%\) after aortic valve closure. In high resolution MRI tagging, the first image that can be used for strain analysis has a delay of 39 ms with respect to the R wave (i.e., beyond the isovolemic contraction), thus missing early contraction events (strain). The early diastolic phase is very important for the LV preload, as shown in recent studies of global longitudinal strain and its predictive value of future outcomes. Early diastolic relaxation is an active energy-dependent process that is rapidly initiated in the basal segments of the LV and propagates towards the apex. Diastolic dysfunction is increased by the abnormal timing of contraction of the ascending limb of the apical VMB. A recent study of the significance of abnormal early diastolic strain on outcomes suggests such a role. In normal situations, it has been demonstrated that mechanical activation and contraction of the lateral wall occur earlier than in the septum, with a late and protracted peak of contraction of the lateral segment; in the septum, it occurs later and peaks earlier. This sequence assures that the lateral wall will not bulge outwards with the early contraction peak of the septum.
the signal starting the earlier contraction of the lateral wall in normal subjects must arrive there via faster mechanoelectric means.\textsuperscript{15} Our data are similar to other significant reports from different ethnic populations.\textsuperscript{15–17}

4.3. Mechanical Implications of Left Axis Deviation

Ventricular electrical remodeling (VER) is triggered by mechanical rather than electrical stimuli via mechanoelectric feedback.\textsuperscript{18,19}

The time course of ventricular electrical remodeling (VER) antecedes the development of hypertrophy.\textsuperscript{16} Ventricular electrical remodeling in late activated segments is triggered by mechanoelectric feedback induced by the change in cardiac activation sequence. VER involves a complex cascade of events that may be initiated by stretch.\textsuperscript{19}

Dysynchronous hearts displayed significantly shorter APDs in the lateral wall relative to the anterior wall (approximately a 16% reduction). Lateral LV segments from LBBB hearts exhibited substantial Cx43 signal lateralization, consistent with VER. Abnormal spatial sequences and/or the displacement of electrical depolarization lead to abnormalities of the sequential strain and strain rate. Mechanoelectric factors lead to abnormal sequences of the regional strain that go beyond the local change of initial depolarization, affecting remote areas of the myocardium. The regional pairing of sections of the ventricular myocardium (in series or in parallel) effects changes and/or im-pairs both ejection and early suction.\textsuperscript{20}

4.3.1. Septal Depolarization

The abnormal septal depolarization noted in LBBB and in LAHB becomes evident by studying the direction, rotation and size of the 10 msec vector, and is the initiating factor of a very specific type of dyssynchrony with LAD the finding on the 12 lead ECG.\textsuperscript{11} In pure RBBB, the 10 msec vector in RBBB is entirely normal. What is now recognized as septal flash,\textsuperscript{21} septal beak\textsuperscript{22} or apical rocking\textsuperscript{23} represents the mechanical expression of an abnormal direction of early septal depolarization. This is present in LAHB alone and in conjunction with RBBB and LBBB with LAD.\textsuperscript{24} An abnormal left axis suggests that a particular variant of abnormal septal repolarization sets in motion a sequence of regional myocardial strain that affects the early isovolumic contraction phase and also the late strain during early relaxation (during which basal segments of LV contract) with implications for the early “suction” phase of LV diastole. Patients with LBBB and a large septal flash (SF) have areas of conduction blocks with a U-shaped activation pattern on non-contact mapping (NCM), and patients with this pattern have favorable acute and chronic responses to CRT.\textsuperscript{21} In patients with a large SF, there may be a block in the proximal left bundle; and accordingly, the endocardium of the LV would be expected to be activated from the RV with a delay of approximately 40–50 ms, caused by slow muscle-to-muscle trans-septal conduction.\textsuperscript{21} The absence of septal flash implies preserved septal activation by the proximal left bundle. It is interesting that 80% of the patients with a large septal flash were non-ischemic.\textsuperscript{21} Apical rocking is more prominent in non-ischemic cardiomyopathy patients.\textsuperscript{23}

The limitations of the study include its retrospective nature, the requirement for hospitalization, coding vari-a-tions on the discharge document, a lack of information regarding the presence of left axis deviation in the LBBB group as well as confounders not included in the analysis, e.g., mechanoelectric feedback, risk factors such as smoking, lipid levels, and medications. An extensive re-view\textsuperscript{25} regarding the pathophysiology of LBBB and a case study by Becker Muscular Dystrophy\textsuperscript{26} stressed the importance of the definition/presence of true LBBB in affecting the response and outcomes of resynchronization therapy. In addition, we did not exclude prior admissions with diag-noses of non-fatal outcomes (MR, AF and HF), although the long follow-up period partiallyameliorates this limitation. The average follow-up of 5.8 years might be too short to demonstrate adverse outcomes, which require longer follow-up to 9.0 years. In a previous smaller study, it was noted that the survival curves did not diverge until approximately 5 years of follow-up.\textsuperscript{4}

5. Conclusions

In patients without apparent ischemic heart disease, the presence of LAHB alone or in combination with RBBB imparts an increased risk of CV and all-cause death compared to isolated RBBB. BFBB is also associated with an increased risk of HF. This study of patients without evidence of ischemic heart disease during follow-up raises the issue of the significance of mechanoelectric factors in determining regional and sequential ventricular strain and its origins on embryology. The noted adverse outcomes with ICBs in non-ischemic patients reported here suggest that functional factors play a role in abnormalities of ventricular pump function (ejection and suction) and raises the possibility that the QRS pattern, in addition to QRS duration, is a primary driver of worse outcomes. To the best of our knowledge, this is the largest reported study comparing ICDs to pure RBBB (without LAD), which has no effect on the initial direction of septal depolarization.

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Conflict of interest

The authors have no conflicts of interest.

References


