Impact of QRS Duration in Heart Failure with Preserved Ejection Fraction

Prabhjot Singh Nijjar, MD1,2; Gateree Ngarmchamnanrith, MD2; Kairav Vakil, MD1; Sherry Pomerantz, PhD2; Darshak Karia, MD2

Abstract

QRS prolongation is a surrogate marker for ventricular dyssynchrony and an independent predictor of mortality in heart failure with reduced ejection fraction (HFrEF). However, the relevance of QRS prolongation in heart failure with preserved ejection fraction (HFPEF) has not been extensively studied. Retrospective chart review of all consecutive patients admitted with a primary diagnosis of acute decompensated heart failure (ADHF) for a period of 1 year at an inner-city community hospital (n=388). Patients were divided into 4 groups on the basis of their ejection fraction and QRS duration. There was high 1-year all-cause mortality (25.7%) in patients presenting with ADHF. There was no significant difference in LOS or 1-year all-cause mortality between patients with HFrEF and HFPEF. In patients with HFPEF, there was higher 1-year all-cause mortality in those with QRS prolongation, though not statistically significant. There is no difference in outcomes of LOS or 1-year all-cause mortality in HFPEF and HFPEF, with QRS prolongation portending a worse prognosis. Further studies are needed to elucidate the etiology of this high mortality in HFPEF.

Keywords — QRS duration, heart failure with preserved ejection fraction (HFPEF), acute decompensated heart failure (ADHF).

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I. INTRODUCTION

Ventricular dyssynchrony due to conduction defects is an independent predictor of mortality in heart failure with reduced ejection fraction (HFrEF) [1-8]. These intra and inter-ventricular conduction defects are apparent on the surface EKG, reflected as QRS prolongation [1]. Thus QRS prolongation (> 120 ms) can be used as a surrogate marker for ventricular dyssynchrony, and occurs in about 30% of patients with HFrEF [2,5]. ACC/AHA guidelines on the management of heart failure recommend resynchronization therapy with biventricular pacing in appropriate patients with HFrEF and QRS prolongation [9]. However, a significant proportion of patients hospitalized with acutely decompensated heart failure (ADHF) have heart failure with preserved ejection fraction (HFPEF) [10-11]. They also frequently have QRS duration >120 ms [12]. The relevance of QRS prolongation in HFPEF has not been extensively studied. We hypothesized that, similar to HFrEF, QRS prolongation is also a risk factor for adverse outcomes in HFPEF.

II. METHODS

Study Objectives
- Describe the demographic and clinical characteristics of patients with HFPEF and QRS prolongation.
- Assess the prevalence of QRS prolongation and its relation to morbidity and mortality in patients with acutely decompensated HFPEF admitted to an inner-city hospital.
- Comparison of morbidity and mortality among four groups divided on the basis of ejection fraction (EF) (< 40% vs ≥ 40%) and QRS prolongation (< 120 ms vs ≥ 120 ms).

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1Division of Cardiology, University of Minnesota Medical School, Minneapolis. 2Department of Medicine, Albert Einstein Medical Center, Philadelphia. Mailing Address: 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455, Email: nijja003@umn.edu

ADHF – acute decompensated heart failure, HFrEF – heart failure with reduced ejection fraction, HFPEF - heart failure with preserved ejection fraction.

Figure 1. Study Flowchart.
Table 1. Demographic data

| Variable   | All N=388 | HFrEF + IVCD N=56 | HFrEF - IVCD N=127 | HFPEF + IVCD N=40 | HFPEF - IVCD N=165 | P value |
|------------|-----------|-------------------|---------------------|-------------------|---------------------|---------|
| Age (years) | 68.0 ± 14.9 | 68.8 ± 14.7 | 62.8 ± 15.3 | 78.9 ± 9.4 | 68.9 ± 14.0 | <0.001 |
| Men (%)    | 49.5 (192) | 66.1 (37) | 59.0 (75) | 50 (20) | 36.4 (60) | <0.001 |
| White (%)  | 11.3 (44) | 8.9 (5) | 6.3 (8) | 25.0 (10) | 12.7 (21) | NS |
| Black (%)  | 81.2 (315) | 78.6 (44) | 86.6 (110) | 70 (28) | 80.6 (133) | NS |
| CAD (%)    | 36.3 (141) | 50 (28) | 36.2 (46) | 35.0 (14) | 32.1 (53) | NS |
| DM (%)     | 44.6 (173) | 37.5 (21) | 40.2 (51) | 45 (18) | 50.3 (83) | NS |
| HTN (%)    | 84.2 (327) | 85.7 (48) | 81.9 (104) | 82.5 (33) | 86.1 (142) | NS |
| CKD (%)    | 25.3 (98) | 44.6 (25) | 15.0 (19) | 20.0 (8) | 27.9 (46) | <0.001 |

Continuous variables expressed as mean ± standard deviation, and categorical variables expressed as percentage (number). HFrEF – heart failure with reduced ejection fraction, HFPEF – heart failure with preserved ejection fraction, IVCD – intra-ventricular conduction defect, CAD – coronary artery disease, DM – diabetes mellitus, HTN – hypertension, CKD – chronic kidney disease. NS = Not significant.

Table 2. Baseline Clinical Data

| Variable   | All N=388 | HFrEF +IVCD N=56 | HFrEF - IVCD N=127 | HFPEF + IVCD N=40 | HFPEF - IVCD N=165 | P |
|------------|-----------|-------------------|---------------------|-------------------|---------------------|---|
| SBP (mm Hg) | 147.1 ± 28.3 | 139.5 ± 27.4 | 142.6 ± 26.4 | 145.4 ± 27.8 | 151.2 ± 29.4 | NS |
| DBP (mm Hg) | 84.4 ± 19.8 | 83.9 ± 18.0 | 86.5 ± 19.7 | 79.6 ± 21.1 | 84.0 ± 20.1 | NS |
| HR (beats/minute) | 88.9 ± 20.7 | 87.1 ± 18.7 | 94.0 ± 20.5 | 77.1 ± 16.5 | 88.5 ± 21.3 | NS |
| Na⁺ (mEq/dl) | 138.1 ± 4.2 | 140.4 ± 5.5 | 138.7 ± 3.3 | 140.2 ± 4.8 | 138.1 ± 5.7 | NS |
| Creatinine (mg/dl) | 1.6 ± 0.3 | 1.4 ± 0.5 | 1.5 ± 0.6 | 1.4 ± 0.5 | 2.0 ± 0.4 | NS |
| EF (%) | 39.9 ± 19.3 | 22.2 ± 8.7 | 22.3 ± 8.3 | 53.6 ± 10.9 | 56.1 ± 10.9 | <0.001 |
| QRS (ms) | 106.1 ± 27.2 | 146.8 ± 20.8 | 95.2 ± 10.6 | 146.1 ± 18.4 | 90.9 ± 12.5 | <0.001 |

All continuous variables expressed as mean ± standard deviation. HFrEF – heart failure with reduced ejection fraction, HFPEF – heart failure with preserved ejection fraction, IVCD – intra-ventricular conduction defect, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, EF – ejection fraction, QRS – QRS duration, NS = Not significant.
Study Design
The study design was a retrospective chart review. All consecutive patients admitted with a primary diagnosis of acute decompensated heart failure (ADHF) for a period of 1 year (July 1st, 2004 to June 30th, 2005) at an inner-city community hospital (Albert Einstein Medical Center, Philadelphia, PA, USA) were identified from the database of all hospital discharges.

A total of 653 HF hospitalizations were identified. Considering only the first admission for HF for each patient, 573 records were selected. Of these, 388 met the study criteria. The study protocol was approved by the Albert Einstein Medical Center Institutional Review Board.

Inclusion criteria: Adults with age > 18 years, admitted to cardiac intensive care or telemetry unit, with principal admitting diagnosis of HF.

Exclusion criteria: Electrocardiogram and echocardiogram not available during the index admission, incomplete discharge summaries, pacemaker or defibrillator present, or assessed not to be in ADHF on chart review.

Study Protocol
Patients were divided into 4 groups on the basis of their EF (< 40% vs ≥ 40%) and QRS prolongation (< 120 ms vs ≥ 120 ms) (Figure 1). QRS width contains more physiological and statistical information as a continuous variable, but the dichotomization at the 120 ms cut-off is more clinically practical. HFrEF was defined as having an EF < 40%, and HFPEF with an EF ≥ 40%.

Data Collection
Data variables on demographic information, presence of co-morbidities, hemodynamic and biochemical values on presentation, EKG and echocardiographic information, and medications on discharge, were collected.

Study End-points
The outcome variables were length of stay (LOS) during the index admission, 1-year readmission rate, 1-year all-cause mortality, and a composite end point of 1-year readmission rate + 1-year all-cause mortality. LOS and readmission rate were assessed from hospital records. All-cause mortality was searched in the Social Security Death Index (SSDI).

Data Analysis
Analysis of variance (ANOVA) for continuous and Chi square for categorical variables was used. A significance level of P<0.05 was considered significantly different. Data analyses were performed using Stata software (StataCorp. *Stata Statistical Software: College Station, TX.*

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### Table 3. Baseline Medications, N=285

| Drug       | All N=285 | HFrEF + IVCD | HFrEF -IVCD | HFPEF + IVCD | HFPEF -IVCD | P       |
|------------|-----------|--------------|-------------|--------------|-------------|---------|
| Nitrate    | 31.2 (89) | 38.1 (16)    | 31.0 (31)   | 21.4 (6)     | 31.3 (36)   | NS      |
| Aspirin    | 71.9 (205)| 61.9 (26)    | 81.0 (81)   | 67.9 (19)    | 68.7 (79)   | NS      |
| Statin     | 44.6 (127)| 45.2 (19)    | 50.0 (50)   | 28.6 (8)     | 43.5 (50)   | NS      |
| Hydralazine| 13.0 (37) | 9.5 (4)      | 19 (19)     | 7.1 (2)      | 10.4 (12)   | NS      |
| Diuretic   | 83.8 (238)| 92.9 (39)    | 83.8 (83)   | 82.1 (23)    | 80.9 (93)   | NS      |
| ACE-i      | 61.8 (176)| 64.3 (27)    | 74.0 (74)   | 53.6 (15)    | 52.2 (60)   | 0.007   |
| β-blocker  | 76.5 (218)| 85.7 (36)    | 84.0 (84)   | 64.3 (18)    | 69.6 (80)   | 0.01    |

All categorical variables expressed as percentage (number). HFrEF – heart failure with reduced ejection fraction, HFPEF - heart failure with preserved ejection fraction, ICVD – intra-ventricular conduction defect, ACE-i – angiotensin converting enzyme inhibitor, NS = Not significant

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III. RESULTS

Overall cohort
The mean age of the overall cohort was 68.0 ± 14.9 years, with 49.5% being men (Table 1). Blacks constituted 81.2%, and whites 11.3%. For the overall cohort of patients presenting with ADHF, the average LOS during the index admission was 5.8 ± 4.8 days, 1-year all-cause mortality was 25.7%, and composite end point of 1-year all-cause mortality and readmission rate was 31.6% (Table 4).

HFrEF vs HFPEF
HFPEF was present in 52.8% of all patients admitted with ADHF (Figure 1). Baseline characteristics were similar among groups, except for age (65.8 ± 14.9 years in HFrEF vs 73.9 ± 12.9 years in HFPEF, P<0.001) and gender (62.5% men with HFrEF vs 43.2% men with HFPEF, P<0.001). Except for a higher prevalence of CKD in HFrEF with QRS prolongation, there was no difference in the presence of co-morbidities across the groups. There was no difference in the hemodynamic and biochemical parameters on presentation between the different groups (Table 2). The mean EF was 22.2 ± 8.5 % in HFrEF, and 54.8 ± 10.9 % in HFPEF. Except for a significantly higher use of beta-blockers (84.8 vs 66.9%, P=0.01) and ACE-inhibitors (69.1 vs 52.9%, P=0.007) on discharge in HFrEF vs HFPEF, there was no difference in prescription of other drug classes between the groups (Table 3). There was no difference in LOS
All patients with HFrEF and HFPEF, whether with typical for our inner biochemical parameters on intr heart failure with preserved ejection fraction, ICVD – only significant trend towards higher heart failure with reduced ejection fraction, HFPEF - heart failure with preserved ejection fraction, LOS – length of stay, NS = Not significant with ADHF, 1 year all cause mortality is very high. Reduced mortality with CRT in selected patients with HFrEF suggests a risk factor effect of QRS prolongation [13], but the prognostic effect of QRS prolongation in HFPEF, and whether CRT might be of benefit, is unknown. Continuous variables expressed as mean ± standard deviation, and categorical variables expressed as percentage (number). Whether QRS prolongation is merely a marker of HF severity or actually a risk factor for HF progression is not clear. Reduced mortality with CRT in selected patients with HFrEF and HFPEF, and this is consistent with other studies [10,11]. Men more commonly have HFrEF and women have HFPEF. Patients with HFPEF tend to be older. Even though the cutoff used of 40% EF may seem low, the mean EF in HFPEF was 54.8%. QRS prolongation was more common in HFrEF, but still present in 19.5% of HFPEF patients.

Table 5. Outcomes (HFrEF Vs HFPEF)

| Outcome | All N=388 | HFrEF N=183 | HFPEF N=205 | P |
|---------|----------|------------|------------|---|
| LOS (days) | 5.8 ± 4.8 | 5.5 ± 4.4 | 6.0 ± 5.2 | NS |
| Readmission Rate | 7.7 (30) | 8.7 (16) | 6.8 (14) | NS |
| 1-year All-cause Mortality | 25.8 (30) | 23.5 (43) | 27.8 (57) | NS |
| Composite End-point | 31.7 (123) | 29.5 (54) | 33.7 (69) | NS |

Continuous variables expressed as mean ± standard deviation, and categorical variables expressed as percentage (number). HFrEF – heart failure with reduced ejection fraction, HFPEF - heart failure with preserved ejection fraction, ICVD – intra-ventricular conduction defect, LOS – length of stay, NS = Not significant.

(5.5 ± 4.4 vs 6.0 ± 5.2 days, P=NS) or 1-year all-cause mortality (23.5 vs 27.8%, P=NS) between patients with HFrEF and HFPEF (Table 5).

**HFrEF and QRS prolongation vs HFPEF and QRS prolongation**

QRS prolongation was present in 24.7% of all patients (30.6% in HFrEF and 19.5% in HFPEF). The mean QRS duration was 146.8 ± 20.8 ms in HFrEF with QRS prolongation, and 146.1 ± 18.4 ms in HFPEF with QRS prolongation. Specifically in those patients with QRS prolongation, there was no difference in LOS (6.1 ± 5.4 vs 5.8 ± 4.0 days, P=NS) or 1-year all-cause mortality (32.1 vs 32.5%, P=NS) between patients with HFrEF and QRS prolongation vs HFPEF and QRS prolongation (Table 6).

**QRS prolongation vs no QRS prolongation**

There was a statistically non-significant trend towards higher 1-year all-cause mortality in patients with QRS prolongation compared to those with normal QRS duration, whether with HFrEF (32.1 vs 19.7%, P=NS), or HFPEF (32.5 vs 26.7%, P=NS).

**Table 4. Outcomes**

| Outcome | All N=388 | HFrEF + IVCD N=26 | HFrEF - IVCD N=127 | HFPEF + IVCD N=40 | HFPEF - IVCD N=165 | P |
|---------|----------|------------------|-------------------|------------------|------------------|---|
| LOS (days) | 5.8 ± 4.8 | 6.1 ± 5.4 | 5.2 ± 3.8 | 5.8 ± 4.0 | 6.1 ± 5.4 | NS |
| Readmission Rate | 7.7 (30) | 14.3 (8) | 6.3 (8) | 2.5 (1) | 7.9 (13) | NS |
| 1-year All-cause Mortality | 25.7 (100) | 32.1 (18) | 19.7 (25) | 32.5 (13) | 26.7 (44) | NS |
| Composite End-point | 31.6 (123) | 41.1 (23) | 24.4 (31) | 35 (14) | 33.3 (55) | NS |

The demographics of our study cohort are typical for our inner city hospital, with a large black populace, and with a high prevalence of hypertension (84.2%). There was roughly an even split between prevalence of HFrEF and HFPEF, and this does not provide information on the cause of death, but given that the cohort did not seem very sick from a HF standpoint, it is possible that the cause of death was associated comorbidities that were not accounted for. Earlier studies had suggested much higher morbidity and mortality in HFrEF compared to HFPEF.

IV. DISCUSSION

Our study shows that in patients admitted to an inner hospital with ADHF, 1-year all-cause mortality is very high. There was no difference in outcomes of LOS or 1-year all-cause mortality in HFrEF and HFPEF, whereas having QRS prolongation portends a worse prognosis.

Whether QRS prolongation is merely a marker of HF severity or actually a risk factor for HF progression is not clear. Reduced mortality with CRT in selected patients with HFrEF and HFPEF, and this is consistent with other studies [10,11]. Men more commonly have HFrEF and women have HFPEF. Patients with HFPEF tend to be older. Even though the cutoff used of 40% EF may seem low, the mean EF in HFPEF was 54.8%. QRS prolongation was more common in HFrEF, but still present in 19.5% of HFPEF patients.

All groups were essentially similar regarding baseline co-morbidities and clinical features. Except for a higher use of guideline recommended beta-blockers and ACE-inhibitors in HFrEF, there was no difference in other medications used. The near normal hemodynamic and biochemical parameters on presentation suggest that these patients may not have been very sick from a HF standpoint. This point will be relevant as we discuss the high overall 1-year all-cause mortality. At the end of 1 year, a quarter of the study population was dead. Our study does not provide information on the cause of death, but given that the cohort did not seem very sick from a HF standpoint, it is possible that the cause of death was associated comorbidities that were not accounted for.
Table 6. Outcomes in QRS Prolongation (HFrEF+IVCD Vs HFPEF+IVCD).

| Outcome                      | All | HFrEF+IVCD | HFPEF+IVCD | P |
|------------------------------|-----|------------|------------|---|
| (days)                       |     |            |            |   |
| LOS                          | 6.0 ± 4.9 | 6.1 ± 5.4 | 5.8 ± 4.0 | NS |
| 1-year All-cause Mortality   | 32.3 (31) | 32.1 (18) | 32.5 (13) | NS |
| Readmission Rate             | 9.4 (9) | 14.3 (8)   | 2.5 (1)    | NS |
| Composite End-point          | 38.5 (37) | 41.1 (23) | 35 (14)   | NS |

However, more contemporary studies report roughly equal, or even higher, mortality in HFPEF [10,11,14]. There was no difference in outcomes between HFrEF and HFPEF in our study. Moreover, there was also no difference in outcomes between HFrEF with QRS prolongation and HFPEF with QRS prolongation. However, in both HFrEF and HFPEF, there was a strong trend towards worse outcomes with QRS prolongation. A recently published large database analysis of the Swedish Heart Failure Registry showed QRS prolongation to be an independent risk factor in HFPEF [15].

Our study has limitations. The retrospective design introduces the potential for confounding. The sample size is relatively small, and hence maybe under-powered to draw conclusions about mortality end-points. Only patients admitted to intensive care and telemetry were included, and they tend to be sicker than patients admitted to regular wards, so the overall mortality could be biased. QRS prolongation comes in different flavors, with left bundle branch block (LBBB) leading to more dyssynchrony and worse outcomes. In our study, the type of QRS prolongation was not reported. Certain variables known to affect HF morbidity such as compliance, follow up, socio-economic status, type of insurance, were not, and maybe cannot be, accounted for. Our study was likely under-powered to detect such a statistically significant difference. Taken together, these data indicate that QRS prolongation maybe an independent risk factor for all-cause mortality also in HFPEF.

V. CONCLUSIONS

1-year all-cause mortality in ADHF is very high. There was no difference in outcomes of LOS or 1-year all-cause mortality in HFrEF and HFPEF, with QRS prolongation portending a worse prognosis. Given the limitations of the retrospective design and small sample size, these findings should only be hypotheses generating. Larger prospective studies are needed to elucidate the etiology of this high mortality in HFPEF.

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