Diabetes Mellitus As a Risk Factor for Right Ventricular Dysfunction and Impact on Mortality

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INTRODUCTION

• Diabetes mellitus is known to increase the risk of heart failure even in the absence of frequently coexisting predisposing/risk factors including coronary artery disease and hypertension.

• Epidemiological data indicate a greater risk of cardiovascular morbidity and mortality in diabetic subjects

• Left ventricular (both systolic and diastolic) impairment in diabetic patients has been well studied.

• The right ventricular (RV) function plays a significant role in the overall myocardial contractility. Nevertheless, most of the previous studies regarding diabetes-induced changes in myocardial dysfunction were dedicated to the left ventricle (LV) at the cost of ignoring the role of the right heart chambers
• In the clinical practice, right ventricular dysfunction is relevant in a variety of diseases affecting both the course and prognosis. Therefore right ventricular performance is also an important issue in diabetic patients.

• The objective of this study is to determine the potential effect of diabetes on right ventricular systolic and diastolic function.

• Right ventricular dysfunction (RVD) is defined as an decreased ejection fraction and/or functional abnormality of diastolic relaxation and filling.

• RVD is known to be an early complication of hypertension and an important predictor of prognosis and mortality in various morbid conditions.
OBJECTIVES

• Determine the potential effect of diabetes on right ventricular systolic and diastolic function.

• Establish the prevalence of right ventricular dysfunction in diabetic subjects.

• Reveal other predisposing risks to right ventricular dysfunction in conjunction with diabetes.

• Determine whether right ventricular dysfunction in diabetes is a benign condition or associated with increased mortality.
METHODS: Study Design

• The objectives of the present study were to evaluate the RV systolic and diastolic functions using conventional echocardiography in patients with DM LV dysfunction.

• This study is a retrospective data analysis of randomly selected patients with and without diabetes mellitus, who had a 2D echocardiogram performed at any Catholic Health System site between 1/2008 and 1/2012.

• We divided our population mainly into diabetic and controls (non-diabetics).
METHODS: Inclusion

• **Inclusion Criteria for Diabetic Subjects:**
  – Establish diagnosis of diabetes mellitus as put forth by the American Diabetic Association.
  – A 2D-Echocardiogram performed between 1/2008 to 1/2012.
  – No clinical and Echocardiographic of LV dysfunction.

• **Inclusion Criteria for Control Subjects:**

  No clinical and laboratory evidence of diabetes mellitus.
  A 2D-Echocardiogram performed between 1/2008 to 1/2012.
  No clinical and Echocardiographic of LV dysfunction
METHODS: Exclusion

• **Exclusion Criteria for All Subjects:**

Any patient who has been diagnosed with LV systolic or diastolic dysfunction
Any patient with Echocardiographic evidence of low LV EF (50%) or HFPEF
Any patient with diagnosis of OSA
Any patient with diagnosis of afib/Valvular disease of heart.
Any patient with diagnosis of COPD.

– **Randomization and Blinding:**
– Both groups will be randomly chosen from Soarian Database and their demographics will be collected as well.
METHODS: Echocardiography

Using the guidelines put forth by the American Society of Echocardiography the following cardiac parameters are assessed:

GUIDELINES AND STANDARDS

Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography

Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography

Lawrence G. Rudski, MD, FASE, Chair, Wyman W. Lai, MD, MPH, FASE, Jonathan Afilalo, MD, MSc, Lanqi Hua, RDCS, FASE, Mark D. Handschumacher, BSc, Krishnaswamy Chandrasekaran, MD, FASE, Scott D. Solomon, MD, Eric K. Louie, MD, and Nelson B. Schiller, MD, Montreal, Quebec, Canada; New York, New York; Boston, Massachusetts; Phoenix, Arizona; London, United Kingdom; San Francisco, California

(J Am Soc Echocardiogr 2010;23:685-713.)
METHODS: Echocardiography

• **RV Systolic Function**
  – RV systolic function has been evaluated using several parameters, namely, RIMP, TAPSE, 2D RV FAC, 2D RV ejection fraction (EF), three-dimensional (3D) RV EF, tissue Doppler–derived tricuspid lateral annular systolic velocity (S0), and longitudinal strain and strain rate.
  – We calculated right ventricular ejection fraction by using Tricuspid Annular Plane Systolic Excursion (TAPSE) measured from the apical four-chamber view at the tricuspid lateral annulus.
  – TAPSE < 16 mm indicates RV systolic dysfunction.
METHODS: Echocardiography

• **RV Diastolic Dysfunction**
  – Assessment of RV diastolic function is carried out by pulsed Doppler of the tricuspid inflow and tissue Doppler of the lateral tricuspid annulus.
  – Right ventricular parameters of diastolic function that include peak early (E) and peak late (A) diastolic flow velocity.
  – A tricuspid E/A ratio < 0.8 suggests impaired relaxation and hence diastolic impairment.
**Statistical Analysis**

- The data are expressed as Mean ± SD and percentages.
  - Student unpaired t-test: Evaluate the differences between the groups
  - Chi-square test: Compare categorical variables
  - Pearson correlation coefficients: Pair the continuous variables. A two-tailed p value < 0.05 was considered significant.

- Several factors differentiated the patients in the 4 groups.
  - Propensity Matching: To evaluate survival with more comparable patients among the diastolic stages. The variables and the propensity models incorporated each of the variables regardless of their significance.
  - Overall and stratified nonparametric survival estimates were obtained via the method created by Kaplan and Meier.
  - A parametric method was used to resolve the number of phases of instantaneous risk for death (ie, hazard function) and to estimate the shaping variables.

- For the statistical analyses, the statistical software Graph pad Prism version 6 was used.
Patients with 2D Echo performed between 1/2008 to 1/2012 and do not meet any exclusion criteria

- 1543 diabetics and 1317 controls

2070 Patients Excluded

- 432 patients with LV systolic or diastolic dysfunction on 2D Echo
- 87 Afib/Valvular Dysfunction on 2D echo
- 304 had one or more of exclusion criteria found on chart review
- 1337 unsatisfactory 2D echo of the right ventricle to fulfill our study criteria

290 Patients Included

136 Diabetics
154 Controls
STUDY DESIGN

• 2860 Patients (1543 diabetics and 1317 controls) who had 2D Echo performed between 1/2008 and 1/2012 were initially selected from the Sorian Clinical data base for screening.
  • This initial selection was done using ICD-9 codes for type 1 and type 2 DM to screen the diabetic group.
  • ICD-9 code used to eliminate patients who had any of the conditions mentioned in the exclusion criteria: CHF, COPD, Afib, various valvular diseases of the heart and OSA.

• 823 Patients were excluded after screening.
  • The screening involved review of the clinical data and 2D echo report from Sorian Clinical data base.

• 1337 Patients were excluded due to unsatisfactory 2D echo of the right ventricle to fulfill our study criteria after revision of the 2D Echo study.

• 290 Patients were included for the study (154 controls and 136 diabetic).

• The clinical data of these patients was obtained using ICD-9 codes from the Sorian clinical data base.

• The right ventricular functional status was obtained by studying the 2D Echo from the data base.
The demographic characteristics and clinical parameters of the participants are depicted in Tables 1. There were no significant differences between the two groups in terms of sex, age, Race, body mass index, and smoking. As expected, the diabetic group had higher mean HBA1C (7.06±1.31) when compared to control subjects (5.75±1.55) which was statistically significant. Also, diabetic group showed a higher percentage of CAD/MI, HTN, CKD and dyslipidemia—all of which were statistically significant.
The echocardiographic and Doppler data of the studied groups are illustrated in Table 2. Tricuspid annular plane systolic excursion (TAPSE), and tricuspid E/A ratio of the diabetic patients (18.15±1.47 vs. 23.12±2.4 and 0.96 ± 0.27 vs. 1.29 ± 0.3, respectively) were significantly lower.
Figure 3. Comparison of number of patients with RVD between two studied groups

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>DM</th>
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</thead>
<tbody>
<tr>
<td>RVD/TOTAL</td>
<td>14/154</td>
<td>29/136</td>
</tr>
<tr>
<td>%</td>
<td>8.68</td>
<td>21.32*</td>
</tr>
</tbody>
</table>

Table 3 depicts number of patients with RVD in control subjects 14 (8.68%) Vs Patients with DM 12 (21.32%).
Table 4. Comparison of RVD subtypes between the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Control/RVD+</th>
<th>DM/RVD+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low TAPSE</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Low E/A</td>
<td>3</td>
<td>17*</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 4 reveals the difference in the types of RVD between the control and diabetic subjects. While control subjects with RVD mainly had a low TAPSE. (compare percentages). In comparison, diabetic patients with RVD mainly had a low E/A ratio. (compare percentages)
Figure 2 depicts total number of patients with low TAPSE and E/A ratio in control subjects 11 (78.5%), 6 (27%) vs patients with DM 12 (41%), 24 (82.75%) respectively.
Table 5. Demographic characteristics of the various subgroups divided on basis of presence or absence of RVD

<table>
<thead>
<tr>
<th>Demographics/Co-morbidities</th>
<th>Control/RVD-</th>
<th>Control/RVD+</th>
<th>DM/RVD-</th>
<th>DM/RVD+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number/Total</strong></td>
<td></td>
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<tr>
<td>Percentage</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>140/154</td>
<td>14/154</td>
<td>107/136</td>
<td>29/136</td>
<td></td>
</tr>
<tr>
<td>91.01%</td>
<td>8.68%</td>
<td>78.67%</td>
<td>22.32%*</td>
<td></td>
</tr>
<tr>
<td><strong>Females (total/age)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>5</td>
<td>53</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>64±17.47</td>
<td>66.51±17.60</td>
<td>67.22±16.78</td>
<td>63.51±17.60</td>
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</tr>
<tr>
<td><strong>Males (total/age)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>72</td>
<td>9</td>
<td>54</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>65±16.43</td>
<td>66.51±17.20</td>
<td>66.22±13.55</td>
<td>62.49±17.20</td>
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</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>24.51±18.99</td>
<td>26.20±10.08</td>
<td>27.33.22±10.64</td>
<td>30.18±12.08*</td>
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<tr>
<td><strong>HBA1C</strong></td>
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<tr>
<td>5.15±1.65</td>
<td>5.6±1.81</td>
<td>7.26±1.74</td>
<td>8.36±1.21*</td>
<td></td>
</tr>
<tr>
<td><strong>CAD/MI</strong></td>
<td></td>
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<tr>
<td>19 (13.57%)</td>
<td>2 (15.35%)</td>
<td>28(26.43%)</td>
<td>8(27.76%)</td>
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<tr>
<td><strong>CKD</strong></td>
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<tr>
<td>15(10.71%)</td>
<td>2 (15.35%)</td>
<td>27(25.84%)</td>
<td>7 (24.13%)</td>
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<tr>
<td><strong>Hypertension</strong></td>
<td></td>
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</tr>
<tr>
<td>40 (28.37%)</td>
<td>4 (30.70%)</td>
<td>52 (48.47%)</td>
<td>7 (79.67%)*</td>
<td></td>
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<tr>
<td><strong>Smoking</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>21 (15.32%)</td>
<td>3 (21.53%)</td>
<td>17 (16.07%)</td>
<td>4 (13.79%)</td>
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<tr>
<td><strong>Dyslipidemia</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>24(16.95%) *</td>
<td>3 (21.53%) *</td>
<td>42(39.23%)</td>
<td>10 (33.53%)*</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>55(39.28%)</td>
<td>7 (5%)</td>
<td>56 (52.33%)</td>
<td>19 (65.55%)*</td>
</tr>
<tr>
<td>American</td>
<td>78 (55.71%)</td>
<td>5 (50%)</td>
<td>47 (44%)</td>
<td>7 (24.18%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7 (5%)</td>
<td>2 (14.28%)</td>
<td>4 (3.7%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
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</tbody>
</table>

*Significant differences
The demographic characteristics and clinical parameters of the patients are depicted in Tables 5. The studied subjects are divided into four subgroups based on presence or absence of RVD. There is a significant difference between the four groups in terms of Race, BMI, mean HBA1C and HTN. Patients with DM and RVD+ have a higher mean HBA1c and BMI. Also, a greater percentage of patients in this group had HTN and belong to AA race. These differences were statistically significant. These results are depicted in figures 3a, 3b, 3c and 3d respectively.
Comparison of BMI between various groups

- Control/RVD- (24.51±18.99)
- Control/RVD+ (25.20±10.08)
- DM/RVD- (27.33±10.64)
- DM/RVD+ (24.51±12.08)

Comparison of HBA1c between various groups

- Control/RVD- (6.15±1.65)
- Control/RVD+ (5.6±1.81)
- DM/RVD- (7.28±1.74)
- DM/RVD+ (8.16±1.21)

Comparison of HTN between various groups

- Control/RVD- (28.37%)
- Control/RVD+ (30.70%)
- DM/RVD- (48.47%)
- DM/RVD+ (79.67%)

Comparison RVD in AA between various groups

- Control/RVD- (39.20%)
- Control/RVD+ (60%)
- DM/RVD- (56%)
- DM/RVD+ (65.55%)
Figure 4 indicates risk factors associated with RVD in diabetic patients. Note 65.51% patients have 3 or more risk factors which a statistically significant association. 31.03% patients with DM and RVD have 3 risk factors and 34.48% have 4 risk factors again a statistically significant association.
CONCLUSION

• Our study indicates that DM is an independent risk factor for development of RVD. High BMI and HBA1c, African American race and HTN are risk factors in diabetic patients for development of RVD.

• RVD in diabetic population is an independent risk factor for mortality. Our study highlights the importance of monitoring right ventricular function in diabetic population especially with additional risk factors.