Evaluation of the Effect of ACE Inhibitor Therapy on Diastolic Dysfunction in Hypertensive Patients

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Abstract
To investigate the effect of optimal control of blood pressure by ACE inhibitor (Captopril) on diastolic dysfunction 100 hypertensive male patient with mean age 38±15 years and 100 normal subjects. The left ventricular diastolic function were evaluated by Echo . study and show diastolic dysfunction in hypertensive patient according to E/A (E: early diastolic velocity, A: Late diastolic velocity with atrial contraction) and isovolumic relaxation time (IVRT), declaration time (DT) the study show reverse E/A ratio, prolong IVRT and DT in hypertensive patient and normal diastolic function in control subject we follow these patient for three months and we reevaluate left ventricular diastolic function were the result still same and diastolic dysfunction still present after three months of good control hypertension with ACE inhibitor drugs. (Captopril).

Introduction
Hypertension constitutes one of the common causes of diastolic dysfunction (D.D) and is a major contributor to the pathogenesis of a large proportion of heart failure cases (Levy et al., 1996). Impaired diastolic function identifies hypertensive patients at increase cardiovascular risk (Schillaci et al., 2002). Its also well known that diastolic dysfunction is usually associated with left ventricular hypertrophy which characterized by a disproportionate involvement of non-myocyte elements(DeMarchi et al., 2000). The studies have shown that diastolic dysfunction may precede the development of left ventricular hypertrophy in hypertensive disease (DeMarchi et al., 2000). With interstitial myocardial fibrosis (Rossi, 1998; Quere Leta et al., 2000; Seccia et al., 2003) and loading being among the most commonly accepted causes.(Leite-Moreira & Correia-Pinto, 2001).

Normal diastolic function allows adequate filling of the ventricles during rest and exercise with out an abnormal increase in diastolic pressures . the initial diastolic event is myocardial relaxation , an active energy-dependent process that causes pressure to decrease rapidly in the left ventricle after the end of contraction and during early diastol .

The normal cycle of cardiac contraction and relaxation requires precise , transient increase and decrease in intra cellular concentration of calcium ions . the sacroplasmic reticulum helps orchestrate the movement of calcium during each contraction and each relaxation (Ebashi, 1997; Mahr et al., 1999).

Calcium ions bind to troponinc, which ultimately disinhibits the inter action of actin and myosin and result in the formation of cross-bridges (Weiss et al., 1976; Brutsaert et al., 1988) . myocardial relaxation is accomplish primarily by removal of calcium ions from troponin C by an enzyme in the sacroplasmic reticulum , called sacroplasmic reticulum calcium adenosine triphosphatase (SERCA2) and sacrolemmal sodium – calcium exchanger .(Hasenfuss, 1998).
Failure of mechanisms of reuptake of calcium ions extruded during contraction can result in the slowing of relaxation or the inability of the cytosolic calcium concentration to return to normal diastolic levels. The latter causes diastolic calcium overload and incomplete relaxation that includes excessive diastolic tension or stiffening (Cain et al., 1998).

**Patient and methods**

This study was done in Merjan teaching hospital in period from January 2009 till January 2010.

One hundred hypertensive male patients with mean age 38±15 year and one hundred normal subjects had been included to evaluate the left ventricular diastolic dysfunction.

All patients originally had Grade 1 essential hypertension (systolic > 140 mmHg) and/or (diastolic > 90 mmHg), with a history of hypertension for more than 1 year. All the hypertensive patients were receiving medical treatment in form of ACE inhibitor capoten (25-50)mg BID.

Patients were excluded if they were not in sinus rhythm, or if they had a history of coronary artery disease, regional wall motion abnormalities, mitral or aortic stenosis, congenital heart disease, cardiomyopathy, mitral or aortic regurgitation, pericardial disease or cor-pulmonale and left ventricular hypertrophy, and they had normal BMI.

The control group consisted of normotensive volunteers, as determined by their blood pressure measurements and medical records. They were asymptomatic and had no known medical problems according to their medical histories and clinical investigations. Control group had same age group and sex and body surface area. All subjects were evaluated for diastolic dysfunction; evaluations were based on known conventional echocardiography criteria.

The diagnosis of diastolic dysfunction was initially based on

- E/A < 1.0
- Deceleration time (DT) > 220 ms
- Isovolumic relaxation time (IVRT) > 100 ms

**Echocardiography:**

Standard two-dimensional and Doppler echocardiograph was used to study all subjects. We used Phillips Envisor version C.O.2 Netherlands B.V. 2005, probe (2-4 MHZ). All subjects underwent resting 12 leads electrocardiogram, careful history routine laboratory tests, physical examination.

We follow those patients for three months after control them blood pressure with ACE inhibitor and we reevaluated the diastolic function by echocardiograph. after three months to see the effect of control blood pressure on diastolic function.

**Result**

The echo cardiological results are presented in table 1 and 2.
Table 1
The mean values of right ventricular and left ventricular end-diastolic and end-systolic dimensions, left ventricular ejection fractions, and left atrial diameters were similar in patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV cm</td>
<td>2.1 ± 1</td>
<td>2.2 ± 1</td>
<td>N.S</td>
</tr>
<tr>
<td>AOD cm</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.2</td>
<td>N.S</td>
</tr>
<tr>
<td>LVEDD cm</td>
<td>4.5 ± 0.1</td>
<td>4.51 ± 0.2</td>
<td>N.S</td>
</tr>
<tr>
<td>LVESD cm</td>
<td>2.70 ± 0.2</td>
<td>2.71 ± 0.2</td>
<td>N.S</td>
</tr>
<tr>
<td>LA cm</td>
<td>3.20 ± 0.1</td>
<td>3.20 ± 0.2</td>
<td>N.S</td>
</tr>
<tr>
<td>LVEF %</td>
<td>65.2 ± 3</td>
<td>66.1 ± 2</td>
<td>N.S</td>
</tr>
<tr>
<td>IVS</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>N.S</td>
</tr>
<tr>
<td>PW</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Table 2
Show significant difference between patients and controls where the patients show diastolic dysfunction as compare to controls in patients E/A ratio reverse, prolong deceleration time (IVRT).

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A</td>
<td>0.85 ± 0.3</td>
<td>1.3 ± 0.1</td>
<td>Sig 0.0001</td>
</tr>
<tr>
<td>IVRT</td>
<td>104 ± 21.4</td>
<td>82.3 ± 21.2</td>
<td>Sig 0.0001</td>
</tr>
<tr>
<td>DT</td>
<td>226 ± 25.2</td>
<td>191.6 ± 31.2</td>
<td>Sig 0.0001</td>
</tr>
</tbody>
</table>

(2)
Result after three months
Still there is no significant difference between patient and control regarding the right ventricular and left ventricular end-diastolic and end-systolic dimensions, left ventricular diameters were similar in patients and controls. (table-1)

Still show significant difference between patient and control where patient show diastolic dysfunction as compare to controls in patients E/A ratio reverse , prolong DT and prolong IVRT. (Table-2)

<table>
<thead>
<tr>
<th>Table 1</th>
<th></th>
<th>Patient</th>
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<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV cm</td>
<td>2.2 ± 1</td>
<td>2.2 ± 1</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>AOD cm</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.2</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>LVEDD cm</td>
<td>4.51 ± 0.1</td>
<td>4.51 ± 0.2</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>LVESD cm</td>
<td>2.70 ± 0.1</td>
<td>2.71 ± 0.2</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>LA cm</td>
<td>3.20 ± 0.2</td>
<td>3.20 ± 0.2</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>IVS</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>N.S</td>
<td></td>
</tr>
<tr>
<td>PW</td>
<td>0.8 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>N.S</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th></th>
<th>Patient</th>
<th>control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A</td>
<td>0.86 ± 0.6</td>
<td>1.3 ± 0.1</td>
<td>Sig 0.0001</td>
<td></td>
</tr>
<tr>
<td>IVRT</td>
<td>105 ± 20.5</td>
<td>82.3 ± 21.2</td>
<td>Sig 0.0001</td>
<td></td>
</tr>
<tr>
<td>DT</td>
<td>227 ± 24.3</td>
<td>191.6 ± 31.2</td>
<td>Sig 0.0001</td>
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</table>
Paired T test was used to determine the difference of patient variability zero time and after three months.

**Discussion**

The main finding of our study is that diastolic dysfunction can be present early in the development of hypertensive disease, before any left ventricular remodeling loading (wall stress) is increased during these early stages, suggesting that it may mean important "co-parameter" in the diastolic dysfunction observed at this point.

Our findings show that diastolic dysfunction may be evident before the presence of left ventricular hyper trophy in patient with systemic hypertension, and there finding are also founded in other studies (Found et al., 1984; Zabalogitia et al., 1998; De Simone et al., 2004; Borges et al., 2006; De Simone et al., 2006).

Exaggerated myocardial fibrosis, (Conrad et al., 1995) intrinsic (Sasaki et al., 2000) myocyte impairment (Yelamarty et al., 1992; Lamb et al., 1999) microvascular ischemia, and loading effects have been described as the principle causes of diastolic dysfunction in systemic hypertension. Mechanical stress forces and humeral substances such as the components of the rennin-angiotensin-aldosterone system, catechol amines, endothelin, nitric oxide, and growth factors have been implicated in mediating myocardial fibrosis (Brilla et al., 1991; Weber, 2000).

Further more, the role of myocardial fibrosis has also been documented by Brilla et al who found that morphometrically determined interstitial and pervascular fibrosis, and not left ventricular hypertrophy was responsible for abnormal myocardial diastolic stiffness.
in rats with genetic hypertension, our study show optimal of blood pressure with captopril had no effect or not improve grade I diastolic dysfunction after three months. In contrast to other studies which show improvement of diastolic dysfunction.

Blood pressure and left ventricular wall thickness both yield an independent (Leite-Moreira & Correia-Pinto, 1999) influence on left ventricular diastolic function it has been shown that the normal ventricle easily compensates for moderate after load evaluations, while greater evaluations induce diastolic dysfunction even in normal hearts.

In contrast, load-dependent diastolic dysfunction occurs in severely diseased hearts even with normal haemodynamic parameters (Grossman et al., 1975).

It had been shown that wall stress after load was higher in the early stages of the left ventricle remodeling than in late stages, suggesting that loading may play an important role in inducing diastolic dysfunction at that stage (Zile & Brutsaert, 2002) that describe the result of diastolic dysfunction not disappear after three months.

Diastolic dysfunction was exaggerated in the late stages possibly mirroring the important role of under ground structural fibrotic lesions.

Some medications directly or indirectly, and especially the calcium blockers and the ACE inhibitors, may have a beneficial effect on diastolic dysfunction.

**Conclusions and Recommendation**

Diastolic dysfunction appears early in hypertensive disease, before the onset of abnormal remodeling or LVH.

Good hyper tension control not releaves the diastolic dysfunction after three months.

Myocardial fibrosis, intrinsic myocyte impairment, microvascular ischemia and loading effects have been described as the principle causes of diastolic dysfunction in systemic hypertension.

Three month may be not enough in future need to 6 months to 1 year.

Tissue Doppler is a sensitive method to detect diastolic dysfunction need to be used in future.

**References**


Borges Mcc, Colombo RCR, Goncalves JGF, Ferreira JDO, Franchini KG. Longitudinal mitral annulus w velocities are reduced in hypertensive subjects with or with out left ventricle hypertrophy. hyper tension (2006) 47:854-60.


