Left Ventricular Mechanics During and After Acute Rheumatic Fever: Contractile Dysfunction Is Closely Related to Valve Regurgitation

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OBJECTIVES

The purpose of this study was to characterize left ventricular (LV) mechanics during acute rheumatic fever (ARF) and to define factors influencing remodeling after the acute event.

BACKGROUND

Acute rheumatic fever is associated with varying degrees of valvulitis and myocarditis, but the impact of these factors on LV mechanics is poorly defined.

METHODS

Echocardiograms and clinical data were reviewed in 55 patients aged 11.2 ± 2.6 years during ARF. Valve regurgitation was absent or mild in 33 (group I) and moderate or severe in 22 (group II). Forty-two children (75%) underwent a further examination after ARF.

RESULTS

Group I patients demonstrated a mildly elevated LV size during ARF and had normal indexes at follow-up. Group II patients demonstrated a markedly elevated LV size (end-diastolic dimension z-score 3.6 ± 1.8, p < 0.01 compared with the normal population) and decreased shortening fraction (z-score −0.8 ± 1.4, p < 0.05). The stress-velocity index, a z-score describing the velocity of shortening-afterload relationship, was normal in group II patients with mitral regurgitation (−0.2 ± 1.2, p = NS) but was depressed in those with aortic regurgitation or both (−1.4 ± 1.4, p < 0.01). At follow-up the stress-velocity index remained depressed (−1.2 ± 1.0, p < 0.01) and had deteriorated in those treated nonsurgically compared with those treated surgically (interval change nonsurgical −0.7 ± 1.2 vs. surgical 1.3 ± 1.3, p = 0.005).

CONCLUSIONS

The evolution of contractile dysfunction during and after ARF is dependent on the degree and type of valve regurgitation and may be influenced by surgical intervention. These findings suggest that mechanical factors are the most important contributors to myocardial damage during and after ARF. (J Am Coll Cardiol 2001;37:201–7) © 2001 by the American College of Cardiology

Acute rheumatic fever (ARF) is a systemic inflammatory illness characterized by varying degrees of synovitis, valvulitis, myocarditis and pericarditis. It is endemic in developing countries (1) and occurs in developed countries especially among socially disadvantaged indigenous and migrant communities (1–4). Chronic rheumatic heart disease with progressive left ventricular (LV) dilatation and dysfunction is the most common form of acquired heart disease and a leading cause of premature death in children and young adults in the developing world (5). A number of factors may contribute to myocardial damage in rheumatic heart disease, including acute or chronic ventricular volume overload and primary rheumatic myocardial involvement.

During ARF, changes in LV size are closely related to the degree of valve regurgitation (6). Left ventricular function is normal in the majority of patients, but, when cardiac decompensation is seen, it is almost always accompanied by severe mitral regurgitation (MR) or aortic regurgitation (AR) (6,7). Although these observations suggest that important myocardial involvement is unusual in the absence of significant valve regurgitation, the relative roles of abnormal ventricular loading conditions and myocardial contractile dysfunction have not been fully explored.

Information regarding myocardial contractile function during and after rheumatic fever is needed to better define the pathophysiology of the disease. Furthermore, an understanding of patterns of recovery of ventricular geometry and the progress of those with myocardial contractile dysfunction are of considerable importance for this patient group where ventricular dysfunction is a significant late complication.

METHODS

Patient population. Fifty-five patients who underwent cardiology review at our institution between April 1994 and May 1997 met the modified Jones criteria for the diagnosis of ARF (8) and had satisfactory two-dimensional and M-mode echocardiographic recordings available for analysis. These 55 patients had echocardiograms at a median of 4 days (range 0 to 60 days) after initial hospitalization for ARF. All had evidence of continuing rheumatic activity.
including elevated acute phase reactants. Mean age at the time of ARF was 11.2 ± 2.6 years (range 4 to 17 years), and 38 (69%) were male. A previous episode of ARF was known and Doppler examinations were recorded on super VHS videotape using commercially available echocardiographic equipment (Hewlett-Packard Sonos 1500 Cardiac Imager). The end-systolic and end-diastolic long axes of the LV cavity were measured in the apical four-chamber view and averaged over three cardiac cycles. High speed (100 mm/s) hard copy two-dimensional directed M-mode recordings of the LV short axis over three to six cardiac cycles were obtained simultaneously with an electrocardiogram, phonocardiogram and indirect carotid artery pulse tracing. Systolic and diastolic blood pressures were obtained as the average of three automated cuff recordings using a Dinamap 845 Vital Signs monitor (Criticon, Inc.).

**Assessment of valve regurgitation.** Regurgitation was graded as none (including physiological or nonholodiastolic MR), mild, moderate and severe using standard criteria. Mitral regurgitation was considered moderate if there was a broad proximal jet filling half the left atrium or attenuation of systolic flow from the pulmonary veins to the left atrium. These criteria, with the addition of systolic flow reversal in the pulmonary veins, were required for the diagnosis of severe MR. Aortic regurgitation was considered to be moderate if the diameter of the regurgitant jet was >20 to 30% of the diameter of the left ventricular outflow tract, in association with diastolic flow reversal in the proximal thoracic descending aorta. In addition to these criteria, diastolic flow reversal in the abdominal descending aorta was required for the diagnosis of severe AR (9–13).

**Assessment of LV mechanics.** The indirect arterial pulse trace and the endocardial borders of the septum and the endocardial and epicardial borders of the LV posterior wall were digitized from the M-mode echocardiogram using customized software and previously described methodology (14,15). End-systole was defined as the time of aortic valve closure and end-diastole as the time of maximum LV chamber dimension. Left ventricle shortening fraction (SF) and the rate-adjusted mean velocity of circumferential fiber shortening (VCFc) were calculated using standard formulae. The LV end-diastolic wall thickness:chamber dimension ratio (EDh/D) was calculated by dividing the end-diastolic posterior wall thickness by the end-diastolic dimension, and the end-diastolic short axis:long axis ratio was calculated as the short axis end-diastolic dimension divided by the long axis end-diastolic dimension. Circumferential wall stress was estimated at end-systole (ESSc) using Mirsky’s formula:

\[
ESSc = \frac{(1.35)(P_{max})(D_{max})(L_{max})}{2(h_{es})[L_{max} + (0.55D_{max}) + (1.1h_{es})]}
\]

where P is pressure in mm Hg, D is dimension cm, L is length in cm, and h is the posterior wall thickness in cm (16).

**Calculation of z-scores relative to the normal population.** The relationship between the end-diastolic dimension and body surface area was determined in the normal population (Table 1). Body surface area-corrected z-scores were then calculated so that the z-score, or normal deviate, represented...
Table 1. Echocardiographic Variables in the Normal Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Equation or Mean</th>
<th>SEE or SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDD (cm)</td>
<td>EDD = 3.88 × BSA(^{+0.409})</td>
<td>0.325</td>
</tr>
<tr>
<td>EDD/D</td>
<td>0.1606</td>
<td>0.0243</td>
</tr>
<tr>
<td>ED SA/LA</td>
<td>0.61</td>
<td>0.05</td>
</tr>
<tr>
<td>SF (%)</td>
<td>33.3</td>
<td>2.74</td>
</tr>
<tr>
<td>VCF(_C) (circ/sec)</td>
<td>1.02</td>
<td>0.084</td>
</tr>
<tr>
<td>ESSc (g/cm(^2))</td>
<td>93.1</td>
<td>13.3</td>
</tr>
<tr>
<td>SVI</td>
<td>VCF(_C) = –0.002 × ESSc + 1.21</td>
<td>0.0804</td>
</tr>
</tbody>
</table>

BSA = body surface area; EDD = end-diastolic dimension; EDD/D = end-diastolic wall thickness:chamber dimension ratio; ED SA/LA = end-diastolic short axis:long axis ratio; ESSc = circumferential end-systolic wall stress; SD = standard deviation; SEE = standard error of the estimate; SF = shortening fraction; SVI = stress-velocity index; VCF\(_C\) = rate-corrected velocity of circumferential fiber shortening.

the number of standard deviations from the normal population mean value. In the normal population there was no relationship between age, body surface area or gender and function indexes (SF and VCF\(_C\), ESSc, EDD/D or the short axis:long axis ratio. Z-scores for these variables were derived relative to the mean value and standard deviation of the normal population (Table 1).

The stress-velocity index (SVI) was calculated as the relation between VCF\(_C\) and end-systolic wall stress and expressed as a z-score relative to the normal relationship. For example, an SVI < -2 indicates a VCF\(_C\) < 2SD below the normal population mean for a given level of ESSc. To account for patients with elevated ESSc, the SVI was obtained by extrapolation of the normal VCF\(_C\) to ESSc relationship using diverging confidence intervals. As ESSc is an index of afterload that relates closely to fiber shortening (17) and VCF\(_C\) is relatively independent of changes in preload (18,19), the SVI is an afterload-adjusted, preload-independent index of contractility (20).

Statistical analysis. Differences between the normal population and groups I and II were examined by one-way analysis of variance, while differences between groups I and II over time were analyzed with repeated measures analysis of variance. The Newman-Keuls multiple comparison test was used to determine individual group differences. Other intergroup differences were analyzed by t-test. Categorical variables were compared by chi-square test and Fisher exact test. Scatter diagrams and then univariate and multivariate linear regression were used to identify factors influencing the SVI during ARF and at follow-up. A p value of <0.05 was considered to be statistically significant.

The study was approved by the hospital ethics committee, and informed consent was obtained from all normal subjects and from patients with ARF in whom echocardiography was not considered part of routine clinical follow-up.

RESULTS

During ARF. Group I patients had a mild increase in LV end-diastolic dimension compared with normal patients, with no difference in the EDD/D (Table 2). The end-diastolic short axis:long axis ratio was increased indicating spherical remodeling. These changes were confined to the subgroup of group I with mild regurgitation; all the above indexes were normal in those with no valve regurgitation. Afterload (ESSc), function (SF and VCF\(_C\)) and contractility (SVI) were normal (Table 2).

Left ventricle mechanics in group II patients were characterized by a marked increase in the end-diastolic dimension and reduction in the EDD/D (Table 2). In addition, ventricular shape was abnormal with a marked increase in the short axis:long axis ratio. Afterload (ESSc) was elevated, while SF and VCF\(_C\) were reduced. The degree of reduction in SF was less than that of VCF\(_C\) (p = 0.047), suggesting preload augmentation of fiber shortening. Because the

Table 2. LV Mechanics During and After ARF

<table>
<thead>
<tr>
<th>Group</th>
<th>During ARF</th>
<th>Mean ± 1 SD vs. Normal</th>
<th>After ARF</th>
<th>Mean ± 1 SD vs. Normal</th>
<th>Repeated Measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group Time Interaction</td>
</tr>
<tr>
<td>EDDz</td>
<td>I</td>
<td>0.6 ± 0.9</td>
<td>↑</td>
<td>0.3 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>3.6 ± 1.8†</td>
<td>↑ ↑</td>
<td>2.0 ± 1.9‡</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>EDh/D</td>
<td>I</td>
<td>0.1 ± 1.0</td>
<td>↑ ↑</td>
<td>0.1 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>-1.0 ± 1.0†</td>
<td>↓ ↓</td>
<td>-0.2 ± 1.2‡</td>
<td>NS</td>
</tr>
<tr>
<td>ED SA/LA</td>
<td>I</td>
<td>0.8 ± 1.3</td>
<td>↑ ↑</td>
<td>0.1 ± 1.0</td>
<td>↑ ↑</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>2.2 ± 1.6†</td>
<td>↑ ↑</td>
<td>1.4 ± 1.9†</td>
<td>↑ ↑</td>
</tr>
<tr>
<td>SFz</td>
<td>I</td>
<td>0.3 ± 1.5</td>
<td>NS</td>
<td>0.1 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>-0.8 ± 1.4*</td>
<td>↓ ↓</td>
<td>-0.5 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>VCFz</td>
<td>I</td>
<td>0.3 ± 1.3</td>
<td>NS</td>
<td>0.1 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>-1.3 ± 1.5†</td>
<td>↓ ↓</td>
<td>-1.0 ± 1.0†</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>ESSc</td>
<td>I</td>
<td>-0.3 ± 1.3</td>
<td>NS</td>
<td>-0.2 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>1.4 ± 1.8†</td>
<td>↑ ↑</td>
<td>-0.4 ± 1.1§</td>
<td>§§</td>
</tr>
<tr>
<td>SVI</td>
<td>I</td>
<td>0.2 ± 1.3</td>
<td>NS</td>
<td>0.1 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>-0.9 ± 1.4†</td>
<td>↓ ↓</td>
<td>-1.2 ± 1.0‡</td>
<td>↓ ↓</td>
</tr>
</tbody>
</table>

\(^{+p < 0.05}\) group I vs. group II; \(^{-p < 0.01}\) group I vs. group II; \(^{\dagger}p < 0.05\) during ARF vs. and after ARF; \(^{\ddagger}p < 0.01\) during ARF vs. after ARF; \(^{\dagger\dagger}p < 0.05\) vs. normal population; \(^{\dagger\dagger}\) or ↑ ↑ \(^{\dagger}p < 0.01\) vs. normal population.

ANOVA = analysis of variance; ARF = acute rheumatic fever; NS = not significant (p > 0.05); vs. normal = p value compared with normal population; z = z-score. Other abbreviations as in Table 1.
reduction in VCFc was greater than could be attributed to the increase in afterload, the SVI was depressed, indicating impaired LV myocardial contractility (Table 2, Fig. 1).

Predictors of LV contractility during ARF. There was a significant relationship between the SVI and the degree of regurgitation (Table 2). Furthermore, depressed contractility (SVI $\leq 2$) was a more frequent finding in patients with moderate or severe valve regurgitation, being detected in 2 of 33 (6%) group I patients compared with 6 of 22 (27%) group II patients ($p = 0.049$). Although group II patients with AR had a similar degree of ventricular dilatation as those with isolated MR (end-diastolic dimension z-score 3.4 $\pm$ 1.6, $n = 12$ [AR] vs. 3.7 $\pm$ 2.0, $n = 10$ [MR]), the reduction in the SVI was largely confined to those with significant AR (Fig. 2). There was no relationship between the SVI and the time between hospital admission and the initial echocardiographic examination, the erythrocyte sedimentation rate, the age at presentation, gender, or initial versus recurrent episode by univariate or multivariate analysis.

After ARF. In group I patients all parameters of ventricular size, function and contractility were normal at follow-up examination (Table 2), and there was no significant difference between the initial and follow-up examinations for any of these variables.

In group II patients there was a tendency for valve regurgitation to improve at follow-up. Of the 14 patients with follow-up data treated nonsurgically, regurgitation improved by at least one grade in 6 (43%). Regurgitation was mild or less in four of the five surgical patients with follow-up data, while it decreased from severe to moderate in one child who underwent mitral valve repair. Hence, 11 patients (58%) demonstrated some degree of improvement in the severity of valve regurgitation, so that 9 had no or mild regurgitation; 5 had moderate regurgitation, and 5 had severe regurgitation at the time of follow-up. Nevertheless, group II patients exhibited persistent LV dilatation (Table 2), albeit to a lesser extent than during the initial examination. End-diastolic wall thickness:chamber dimension ratio had normalized as had ESSc, the latter being significantly lower compared with the initial examination. Although SF had also normalized, VCFc remained depressed so that the SVI was reduced, indicating a persistent impairment of LV contractility (Table 2).

Predictors of LV myocardial contractility after ARF. As was the case during ARF the degree of valve involvement at presentation was an important predictor of the SVI at the follow-up examination (Table 2). Furthermore, an abnormal SVI ($\leq 2$) was observed in no group I patient compared with 5 of 19 (26.3%) group II patients ($p = 0.01$).
There was no significant relationship between the SVI and age, gender, or the interval between the initial examination and follow-up examination by univariate or multivariate analysis.

**Impact of surgery on LV contractility in those with moderate or severe regurgitation.** The five patients who had valve replacement or repair had a lower end-diastolic diameter at follow-up when compared with those who did not undergo surgery (Table 3). Although the follow-up SVI was not significantly different between the surgical and nonsurgical groups, it had deteriorated significantly between the initial and follow-up examination in the nonsurgical group. In contrast it tended to improve in the surgical group (Table 3). Thus, the change in SVI was different in the two groups (change in SVI −0.7 ± 1.1 [nonsurgical] vs. 1.3 ± 1.3 [surgical], p = 0.005). On further analysis of the nonsurgical group, those whose regurgitation was unchanged at follow-up had a significantly lower SVI when compared with those with a spontaneous improvement in the degree of regurgitation (−1.9 ± 0.3 vs. −0.8 ± 0.6, p = 0.03). Thus, the progressive contractile dysfunction in the nonsurgical group was largely confined to those with persistent significant valve regurgitation. It was not related to the initial severity of the valve lesion (moderate vs. severe) or the valve affected (aortic vs. mitral).

**DISCUSSION**

This study demonstrates that myocardial contractile function is closely related to the degree of valve regurgitation during ARF. When regurgitation is mild, changes in LV size and shape were minimal, and indexes of fiber shortening, afterload and contractile function were normal. At late follow-up ventricular size, shape and function were normal.

In contrast, those with more severe valve lesions had marked abnormalities of LV geometry and function. Left ventricle dilation was accompanied by a reduction in the LV wall thickness:chamber dimension ratio indicating a poorly compensated volume load. Indexes of function (SF and VCFC) were depressed, and both preload (as indicated by the discrepancy between the SF and VCFC) and afterload were increased. Importantly, when corrected for afterload, the velocity of shortening remained depressed, indicating impaired ventricular contractility. At follow-up group II patients demonstrated a reduction in the severity of valve regurgitation, a reduction in the degree of LV dilatation and normalization of afterload. Nevertheless, both VCFC and SVI remained depressed, indicating a persistent reduction in myocardial contractility. Preload augmentation of ventricular function masked a significant impairment in the LV contractile state, demonstrating the importance of accounting for loading conditions when assessing myocardial contractility in this patient population.

A number of factors may detrimentally affect LV myocardial contractility during ARF. These include primary rheumatic myocardial involvement with myocyte damage and fibrosis (21,22) and myocardial damage secondary to sudden increases in ventricular volume and afterload associated with the acute onset of MR or AR. Chronic volume load associated with longstanding valve regurgitation may also contribute (23–26), given that previous episodes of rheumatic fever may be undiagnosed. In addition, primary myocardial involvement, as evidenced by histological abnormalities of the myocardium, has been well documented during ARF (21,22). Nevertheless, its impact on the contractile state of the myocardium during the acute phase of the illness and its long-term importance is poorly understood and remains controversial (6,7,21). In this study myocardial involvement appeared clinically unimportant in those with little or no echocardiographic manifestation of valvulitis, while the ventricular remodeling and contractile dysfunction seen in those with more significant valve lesions can be attributed to mechanical factors secondary to valve regurgitation.

**AR versus MR.** During ARF depressed contractility was largely confined to those patients with significant AR, either as an isolated lesion or in combination with MR. This disparity can be explained by differences in the pathophysiology of acute or subacute AR and MR. In animal models acute MR is associated with normal or reduced wall stress. Consequently the velocity of shortening often increases and contractility is maintained (27,28). Over time a chronic volume load will result in a progressive reduction in contractile function as was seen at the follow-up examination in this study. In contrast, the increased end-systolic pressure and increased wall stress evident during acute AR is associated with a reduction in the velocity of shortening (27,28).

### Table 3. Group II Patients Treated With (n = 5) and Without (n = 14) Surgery

<table>
<thead>
<tr>
<th></th>
<th>During ARF</th>
<th>After ARF</th>
<th>Repeated Measures ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± 1SD</td>
<td>Mean ± 1SD</td>
<td>Group</td>
</tr>
<tr>
<td>EDDz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>3.1 ± 1.8</td>
<td>2.6 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>4.5 ± 1.6</td>
<td>0.2 ± 0.8*</td>
<td></td>
</tr>
<tr>
<td>SVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>−0.7 ± 1.4</td>
<td>−1.4 ± 1.0†</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery</td>
<td>−2.0 ± 1.2*</td>
<td>−0.7 ± 1.1</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 comparing no surgery vs. surgery; †p < 0.05 during ARF vs. after ARF; ‡p < 0.01 during ARF vs. after ARF.

The analysis excludes three patients with no available follow-up data.
Elevated wall stress increases myocardial oxygen demand while tachycardia and diastolic hypotension compromise oxygen delivery. This combination of events likely explains the prevalence of contractile dysfunction for patients with significant AR.

**Surgical intervention.** The number of patients treated surgically was small, but the dependence of contractile dysfunction on mechanical factors is further demonstrated by the differences between the surgical and nonsurgical groups at follow-up. Those who underwent valve surgery had no further deterioration in contractility, while those who did not demonstrated a progressive decline, particularly if the degree of regurgitation remained significant. These data are in concordance with those of Essop and coworkers (7) who found a normal shortening fraction after valve replacement surgery for patients with ARF.

In our experience, and in that of others (29), valve surgery during ARF conveys a high likelihood of valve replacement. Because of this we have restricted surgical intervention to those with persistent heart failure despite bed rest and medical treatment. However, the favorable influence of valve surgery on the evolution of contractile dysfunction suggests that a low or declining stress-velocity relationship may also be an indication for surgical intervention. Such a strategy appears appropriate given that myocardial contractile function is an important predictor of long-term outcome for patients with valve regurgitation (23,30,31). Nevertheless, numbers in this study are small, and further investigation is needed to establish indications for surgery during ARF.

**Study limitations.** Initial studies were undertaken during ARF. In some instances this was after a period of hospitalization at another institution, and the study was performed some time into the acute illness. There was no association between any of the measured echocardiographic parameters and time from admission to a hospital, indicating that this factor is unlikely to have influenced the findings of this study. Similarly, the diagnosis of recurrent rheumatic fever may be difficult to make with certainty. We have combined patients who had a known recurrence with those in whom a recurrence was suspected by history; there may be others who had previous, undiagnosed episodes of rheumatic fever. Again, the lack of correlation between recurrence and echocardiographic parameters suggests this factor is not an important confounding variable.

Finally, the SVI was derived from comparison of the relationship between ESSc and VCFc with that of the normal population. Practical and ethical difficulties have prevented us from obtaining normal data at elevated afterload in this age group. At the initial examination a number of group II patients had elevated end-systolic wall stress, and the SVI for these patients was obtained by extrapolation of the normal data. Confidence intervals for the wall stress-velocity of shortening relationship may be less accurate under these circumstances. Importantly, afterload was elevated in only one patient at the follow-up examination.

Furthermore, there was no relationship between the change in SVI and change in afterload, indicating that alterations in the SVI were unlikely to be related to misrepresentation of the stress-shortening relationship.

**Conclusions.** During ARF, LV contractile function is closely related to the degree of valve regurgitation, and contractile dysfunction is uncommon when there is no significant valve lesion. The dependence of contractility on the degree and type of regurgitation and on surgical intervention suggests that mechanical factors—acute and chronic volume and pressure loading—are the major contributors to myocardial damage.

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### REFERENCES