Revisiting methods for assessing and comparing left ventricular diastolic stiffness: impact of relaxation, external forces, hypertrophy, and comparators

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CONTROVERSIES OVER THE PATHOPHYSIOLOGY of heart failure with diastolic dysfunction (HFdi) include whether the disease state is defined by ischemia, ventricular remodeling, or a combination of these factors (1, 2). Although previous studies have focused on relation-ship and position using parametric methods used to compare its shape and position using parametric methods used to characterize diastolic function but can be influenced by external forces (pressure exerted on the LV by the right heart chambers and the pericardium) (7, 14), active ventricular relaxation (23, 27, 28), the number of data points used to define the diastolic PVR, and the operating LV volume at which the SB data are collected (11). Although numerous studies have documented the effect of the right heart and pericardium on the holodiastolic PVR (1, 4), the effect of these extrinsic forces may be diminished in the presence of septal (17) or concentric (30) LV hypertrophy. Although the impact of relaxation on the SB method can be minimized with mathematical modeling to correct early diastolic pressures for the contribution of impaired relaxation (28, 37), direct comparisons of the “relaxation-corrected” single beat (RC-SB) and the MB method have not been reported. Furthermore, clinical studies characterizing diastolic function must often rely on echocardiographic or angiographic assessment of LV volume where a limited number of diastolic volume points are used to characterize the PVR. The impact of such restrictions on the accuracy of the PVR has not been assessed.

In addition to the methods used to construct the PVR, the methods used to compare its shape and position using parametric methods used to characterize diastolic function but can be influenced by external forces (pressure exerted on the LV by the right heart chambers and the pericardium) (7, 14), active ventricular relaxation (23, 27, 28), the number of data points used to define the diastolic PVR, and the operating LV volume at which the SB data are collected (11). Although numerous studies have documented the effect of the right heart and pericardium on the holodiastolic PVR (1, 4), the effect of these extrinsic forces may be diminished in the presence of septal (17) or concentric (30) LV hypertrophy. Although the impact of relaxation on the SB method can be minimized with mathematical modeling to correct early diastolic pressures for the contribution of impaired relaxation (28, 37), direct comparisons of the “relaxation-corrected” single beat (RC-SB) and the MB method have not been reported. Furthermore, clinical studies characterizing diastolic function must often rely on echocardiographic or angiographic assessment of LV volume where a limited number of diastolic volume points are used to characterize the PVR. The impact of such restrictions on the accuracy of the PVR has not been assessed.

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Thus our objective was to compare the SB, the RC-SB, and the MB methods of assessing diastolic stiffness during conditions in which changing relaxation impairment and pericardium-mediated external forces could influence the SB PVR, in the absence and presence of LV hypertrophy and accounting for covariance of α and β in comparisons. Furthermore, because clinically invasive studies often obtain a limited number of pressure and volume points, the impact of fitting a limited number of data points to the exponential PVR equation was assessed.

METHODS

All experimental procedures were designed in accordance with National Institutes of Health guidelines and approved by the Mayo Institutional Animal Care and Use Committee.

Study Design

Included in the study were 26 mongrel dogs (20–30 kg body wt), which were studied in the anesthetized, open-chest state with simultaneous high-frequency pressure-volume measurements. Seven young normal (YN) (age <2 yr old) dogs and 7 old hypertensive (OH) (age 8–12 yr old) dogs with an intact pericardium were studied at three loading conditions: at baseline, after acute increases in afterload with intravenous phenylephrine (2.5 μg/min) infusion to achieve a systolic pressure ≥180 mmHg, and after volume expansion with intravenous dextran (500 ml over 30 min). To isolate the effects of the pericardium, a separate group of six YN and six OH dogs with an open pericardium were studied after a similar volume expansion (500 ml of dextran).

Dogs included in the present study were selected from two different studies that examined aspects of ventricular and vascular structure and function, which have been previously reported (22, 29). All pressure-volume data used in the analyses were acquired with breathing held (ventilator turned off) at end expiration.

Hypertensive Dog Model

The bilateral renal wrap model was used to induce chronic hypertension as previously described (10, 22). An in-dwelling arterial port was placed in the femoral artery for blood pressure monitoring. Dogs were studied after 8 wk of hypertension.

Hemodynamic Studies

All dogs were studied under fentanyl (0.25 mg/kg followed by 0.18 mg·kg⁻¹·h⁻¹) and midazolam (0.75 mg/kg followed by 0.59 mg·kg⁻¹·h⁻¹) anesthesia. Via left thoracotomy, a pneumatic occluder (In Vivo Metrics, Heraldsburg, CA) was placed around the inferior vena cava (IVC) adjacent to the right atrium and used for acute IVC occlusion. A transonic flow probe (Transonic Systems, Ithaca, NY) was placed around the ascending aorta to quantitate the flow in dogs studied with a conductance catheter. An atrial pacing lead was used to pace at 10–20 beats/min above sinus rate. The pericardium was not perturbed during this instrumentation.

In studies with intact pericardium, a 7-Fr conductance catheter (Millar or CD Leycom catheters and CD Leycom processor, Zoetermeer, The Netherlands) was introduced through the femoral artery and positioned in the LV by echocardiographic guidance (3). In studies with open pericardium, ultrasonic piezoelectric crystals (2.0 mm; Sonometrics, London, ON, Canada) were placed on the apical, posterior, and anterior endocardial LV surface and basal midmyocardial surface for measurement of the long- and short-axis dimensions with LV volume calculated as \((\pi/6)(\text{long axis})(\text{short axis})^2\) (18). Simultaneous LV pressure was recorded with a high-fidelity micromanometer-tipped catheter (Millar Instruments, Houston, TX) advanced through the femoral artery.

All dogs received propranolol (2 mg/kg) and atropine (1 mg) for autonomic blockade before data collection. All data were acquired at 250 Hz with respiration briefly suspended at end expiration. For IVC occlusions, data were collected for two to four beats before and again during IVC occlusion. Pressure transducers were calibrated with strain gauge transducers before use and matched to fluid-filled pressure in situ. The conductance signal is converted to LV volume \([V = (1/A)(p)(L)^2(G - G_p)]\), where \(A\) is the slope factor, \(p\) is the specific resistivity of blood measured from a 5-ml blood sample, \(L\) is the distance between electrodes, \(G\) is total conductance, and \(G_p\) is the parallel conductance. \(G_p\) was determined via the hypertonic saline method, and \(A\) was derived by comparing the conductance-determined stroke volume with the aortic flow probe stroke volume (3). Calibration of the catheter (\(p, G_p, A\)) was repeated after volume expansion.

Dogs were euthanized by intravenous KCl, consistent with guidelines of the Panel on Euthanasia of the American Veterinary Medical Association.

Pressure-Volume Analysis

**MB analysis.** Digital data were acquired at 4-ms intervals and analyzed with customized software (SonoSOFT; Sonometrics). End-diastolic PVR estimation by MB analysis was done as previously described (8) and as shown in Fig. 1A. End diastole was defined as the peak of the R wave on the ECG. End systole was defined as the upper left corner of the pressure-volume loop. The EDP-volume data points were fit to the monoequivalent equation \(\text{EDP} = \alpha e^{bt} + \text{EDV} (6)\) using least-squares nonlinear regression. Each end-diastolic PVR defined by the MB method was carefully inspected for evidence of influence by external forces as evident from an initial drop in EDP without corresponding decline in EDV (<3% decrease in EDV) as previously described (7). Where an effect of external forces was evident, those beats were excluded from the end-diastolic PVR data.

**SB analysis.** Estimation of diastolic PVR using SB analysis was performed on a single representative beat just before IVC occlusion. Recognizing that diastolic pressures during an SB may be affected by both LV passive diastolic stiffness and ongoing relaxation (28), the observed diastolic PVR was corrected for relaxation pressure (Fig. 1B); the time constant of isovolumic relaxation (\(\tau\)) was first calculated with the method of Weiss et al. (35), assuming zero asymptote. A theoretical relaxation pressure was then calculated from the following equation: relaxation pressure \(= P_0e^{-(t - t_0)/\tau}\), where \(P_0\) and \(t_0\) are the pressure and time, respectively, at the negative peak of the first time derivative of LV pressure (peak negative dP/dt). The final corrected LV pressure was obtained as follows: corrected LV pressure = observed pressure − relaxation pressure. The corrected pressure and corresponding LV volumes after the point of minimal observed LV diastolic pressure were fit to the monoequivalent equation (corrected \(P\) = \(\alpha e^{bt}\) volume) with least squares regression, providing the SB \(\alpha\) and \(\beta\). This method will be termed RC-SB.

Because continuous volume measurements in humans usually require the use of conductance catheters, such a method has been infrequently used in clinical studies. Some investigators have, instead, used the more practical approach of choosing three diastolic volume points calculated with a combination of two-dimensional and Doppler echocardiography (37). To test the accuracy of determining the diastolic PVR from only three points, we chose the following data points: the minimal diastolic pressure corrected for relaxation, the pressure just before atrial contraction, and the EDP; these were plotted against their respective volume points, and \(\alpha\) and \(\beta\) were calculated from fitting those points into the same monoequivalent equation. This method will be termed three-point RC-SB and was tested on YN and OH dogs with intact pericardium before volume expansion, under different afterload levels.

An uncorrected SB PVR was also calculated by simply using the relationship between the observed LV diastolic pressure and the
is covariance between the derived
term SB.

The regression line (EDP
methods.

As recently emphasized by Burkhoff et al. (6), for each set of
PVR data sets can have different
other SB techniques were assessed. Linear least-squares regression
analysis was used for correlation.

RESULTS

Group Characteristics

The conscious OH dogs had chronically elevated blood
pressures similar to results observed previously (10, 22); how-
ever, in all dogs, blood pressure results were lower in the
anesthetized, open chest, and postinstrumentation state (data
don not shown). On the selected beats or IVC occlusions, the
systolic blood pressure in all dogs varied from 110 to 169
mmHg at baseline and from 185 to 236 mmHg with phenyle-
ephrine infusion. The EDP varied from 6 to 32 mmHg. The
total period of active relaxation relative to the diastolic period
on the selected beats varied widely (range 23–103%), depending
on the degree of relaxation impairment (which varied with
LV systolic pressure and heart rate), heart rate, and systolic
duration. The LV ejection fraction in all dogs at the time of the
study was 48 ± 12%.

RC-SB vs. MB Method in YN and OH Dogs at Baseline and
During Pressure Loading

In dogs with intact pericardium studied at baseline (YN and
OH) or after phenylephrine infusion (OH+PE), visual inspection
showed that the diastolic PVR from the RC-SB and MB
methods appeared superimposable. The pressure-volume data
from representative YN, OH, and OH+PE dogs are shown in Fig.
2. Although the diastolic pressure-volume data overlap and
the monoexponential regression lines appear similar, the derived
β and α are not identical, with only modest correlation and poor
agreement between values derived from the RC-SB and MB PVR
data (Fig. 3, A and B). Results were similar when the SB data were
restricted to the same volumes as the MB data (data not shown),
EDV10–30 values, however, showed excellent correlation and
agreement between RC-SB and MB PVR (Fig. 3C).

In the dogs with intact pericardium, before volume expa-
sion, the uncorrected SB PVR would either not fit a mono-
exponential relationship (as evident in Fig. 2, A and C) or be
inaccurate. When data could be fit, the β calculated was
typically lower than the MB β (0.038 ± 0.027 vs. 0.087 ±
0.05; \(P = 0.0004\)), and α was typically higher (4.54 ± 4.6 vs.
0.99 ± 1.0; \(P = 0.002\)). The EDV10–30 stiffness parameters
also differed significantly between groups, being larger (de-

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Fig. 1. Characterization of end-diastolic pressure (EDP)-volume relationship
(PVR) by multiple-beat (MB) and relaxation-corrected single-beat (RC-SB)
methods. A: MB method, with simultaneous pressure and volume measurement
during caval occlusion to reduce preload. The regression line (EDP =
αeβ•volume, shown in red) that best fits the end-diastolic points represents the MB
end-diastolic PVR. Inset: higher pressure scale. B: RC-SB method. The solid
line is the left ventricular (LV) pressure vs. time, starting at the beginning of
diastole. The dashed line is the extrapolation of the isovolumic relaxation
pressure period after a zero-asymptote monoexponential decay, forming the
“relaxation pressure.” The red line is the “corrected pressure,” obtained by
subtracting the relaxation pressure from the observed pressure. This corrected
pressure is then plotted against the instantaneous volume (inset) and fitted in a
monoexponential PVR, displayed in blue. Only points after the minimally
observed LV diastolic pressure was reached were included in the fit.
creased stiffness) by the uncorrected SB method (Fig. 4), consistent with the higher early diastolic LV pressures present when not corrected for the effect of relaxation.

Three-Point RC-SB vs. MB Method in YN and OH Dogs at Baseline and During Pressure Loading

In dogs with intact pericardium studied at baseline (YN and OH) or after phenylephrine infusion (OH PE), the three-point RC-SB method commonly overestimated \( \beta \) (0.10 ± 0.03 vs. 0.084 ± 0.05; \( P = 0.025 \)) and underestimated \( \alpha \) (0.40 ± 0.35 vs. 1.06 ± 1; \( P = 0.0008 \)) compared with the MB method (Fig. 5, A and B). Although the EDV\(_{10-30}\) obtained from the three-point SB method correlated well with those obtained from the MB method (Fig. 5C), the agreement was not perfect, with small but statistically significant differences in EDV\(_{10-30}\) between the two methods (\( P < 0.05 \)).

Effect of External Forces

In YN and OH dogs with intact pericardium, at baseline, the effect of external forces on the EDP was minimal (1 ± 0.8 mmHg in YN and 0.8 ± 0.6 mmHg in OH animals), as assessed by the acute drop in EDP with minimal drop in EDV (<3%) immediately after IVC occlusion. After acute volume expansion with intact pericardium, the EDP increased by 12 ± 5 mmHg and EDV increased by 18 ± 13 ml (from a baseline of 37 ± 9 ml), whereas heart rate was not changed (+0.6 ± 2 beats/min). This was associated with evidence of an effect of extrinsic forces on diastolic pressures as the acute drop in EDP without change in EDV increased to 6.2 ± 4.3 mmHg in YN and 6.0 ± 4.1 mmHg in OH (\( P < 0.01 \) compared with before volume expansion; \( P > 0.5 \) when OH vs. YN are compared). Reflecting the enhanced effect of extrinsic forces after acute volume expansion, correlation between \( \beta \) (\( r = 0.73, P = 0.02 \)) and \( \alpha \) (\( r = 0.2, P = 0.60 \)) derived from the MB and SB methods after acute volume expansion was weaker and agreement was poor (data not shown). There was still good correlation between the EDV\(_{10-30}\) stiffness measures derived from the two methods (Fig. 6A). However, the RC-SB method yielded smaller EDV\(_{10-30}\) results (Fig. 6, A and B).
A representative example of the pressure-volume data from an OH dog after volume expansion is shown in Fig. 6C. Over the first five beats obtained during IVC occlusion, the EDP falls by 6 mmHg without reduction in EDV. The abrupt parallel drop in EDP without drop in EDV during early IVC occlusion reflects the effect of external forces on EDP (7). If these data points were included in the MB PVR, the $\beta$ would be falsely elevated. However, even after appropriately excluding beats influenced by external forces from the MB PVR, the RC-SB diastolic pressure data remain higher than the MB EDP data over the range of diastolic volumes. Although the steepness of the diastolic PVR defined by the SB method is lower, the $\beta$ is lower, the position of the relationship is shifted upward, the $\alpha$ is higher, and the EDV$_{10}$ is lower.

In contrast, in YN and OH dogs studied in the absence of the pericardium, after an identical acute volume expansion (raising EDV by 14 ml from a baseline of 42 ml; $P = 0.3$ compared with dogs with intact pericardium), the diastolic PVR was similar by the relaxation-corrected SB and MB methods (representative example in Fig. 7A), as indicated by similar EDV$_{10-30}$ (Fig. 7B). The correlations between estimates of stiffness from the two methods using $\beta$ ($r = 0.87$, $P = 0.0006$) and $\alpha$ ($r = 0.75$, $P = 0.008$) were not as strong, and agreement was weaker (data not shown).

DISCUSSION

The main findings from the present study are as follows: 1) if diastolic pressure points are corrected for the effect of ongoing relaxation, SB data can substitute for the MB technique in constructing the diastolic PVR in normal and hypertensive hearts over a wide range of afterload levels; 2) a stiffness measure incorporating information from both $\beta$ and $\alpha$ enhances the ability to describe the position of the diastolic PVR in a single number and facilitates comparison of PVR between groups or methods; 3) as expected, SB analysis may overestimate stiffness in the presence of acute volume overload, as SB data are influenced by external forces mediated by the presence of the pericardium; 4) although external forces also affect the end-diastolic PVR, as defined by the MB method, this confounding effect can be recognized and corrected with the use of careful examination of the data; and 5) stiffness measures derived from the RC-SB PVR using a limited number of data points still correlate fairly well with those derived from the MB method. These findings illustrate that accurate assessment of diastolic properties can be obtained without acute preload reduction if limitations and confounding factors are carefully accounted for.

SB Method as Used in Prior Studies

The SB method has been used by some investigators to estimate LV diastolic stiffness measures without correcting for relaxation; common methods include dividing the difference between minimal and end-diastolic LV pressures by the corresponding change in volume (15, 19, 25) and calculating the slope of the derivative of the active diastolic pressure vs.
volume (33). These methods do not account for the effect of relaxation at the beginning of LV filling and, as we also demonstrate, can be inaccurate, especially when relaxation is prolonged. Pak et al. (27) demonstrated that the diastolic PVR from SB analysis was very discordant from the passive PVR calculated from the MB method during IVC occlusion in patients with hypertrophic cardiomyopathy. Although correction for the effect of relaxation was not performed and may explain this finding, it is possible that hearts with hypertrophic cardiomyopathy exhibit a diastolic behavior different from normal or hypertensive hearts. Whereas Kawaguchi et al. (14) suggested that SB and MB methods were discordant in patients with HFnlEF, their study did not correct for the impact of impaired relaxation and did not compare the SB and MB PVRs using parameters accounting for covariance in $\alpha$ and $\beta$.

Correcting for the Effect of Relaxation on the SB Diastolic PVR

With the limitation of using the uncorrected diastolic limb of the SB pressure-volume loop, previous investigators have used a mathematical model to correct for the impact of active relaxation on early diastolic pressures and used this method to construct the diastolic PVR from a single beat in patients with HFnlEF (28, 37). Although this method was based on an elegant combination of theoretical and experimental work and generated convincing clinical data, it has not been formally validated against the MB method.

Our findings support the validity of the RC-SB method for constructing the diastolic PVR and extend previous studies by showing that PVR defined by this method appears similar to PVR defined by the MB method, in both normal and hypertensive hearts and over a range of afterloads. The expected limitations with acute volume overload in the presence of the pericardium are also demonstrated. We further extend these previous studies by demonstrating that the agreement between the two methods, obvious on visual inspection of the PVRs, may not be reflected when the usual derived stiffness indexes ($\alpha$ and $\beta$) are used to compare the PVRs. However, agreement between the two methods is apparent when alternative indexes derived from the PVR data are employed as discussed below.

Comparing LV Diastolic Properties

It is not only the method used to construct the PVR that is important but also the statistical analysis used to compare PVR between methods, between groups of patients, or before and after therapeutic intervention. It is a common practice to use $\beta$ for this purpose, and this is often adequate but can be inaccurate, depending on the nature of the specific data sets. As demonstrated here, there is a strong, nonlinear, and inverse covariance between the two numbers. Although the EDV calculated from an arbitrary EDP and the PVR-derived curve-fitting constant and stiffness coefficient can represent an extrapolation of the available diastolic PVR to an arbitrary EDP, the value of the parameter is that it expresses information regarding both $\alpha$ and $\beta$ and both the shape and/or position of
The potential importance of this type of stiffness or “capacitance” index is also underscored by the fact that clinically significant differences in $\beta$ between groups (or before and after therapy) can be relatively small in magnitude (37), whereas the reported variability in $\beta$ as measured in vivo studies is often large (14), likely reflecting the covariance between $\alpha$ and $\beta$ and the fact that in vivo PVR data are not perfectly monoexponential. In situations in which directional changes in $\alpha$ and $\beta$ may be discordant (i.e., higher $\beta$ but somewhat lower $\alpha$ between groups), calculation of the EDV$_{10-30}$-type variable can help confirm the validity of the changes indicated by $\beta$. Finally, it is increasingly recognized that changes in “distensibility,” where the diastolic PVR is shifted upward without a significant change in its shape, can occur in clinically relevant situations (5). This type of change would not be reflected by a change in $\beta$.

On the other hand, the capacitance index, calculated as EDV$_{10-30}$, should not be used as the only way to describe the diastolic PVR. Other methods can also be used for this purpose. For example, a multivariable linear regression analysis can be performed with $\beta$ as a dependent variable, while accounting for the logarithm of $\alpha$ in the comparison.

Impact of Limited Number of Pressure-Volume Points on the RC-SB Method

Use of a limited number of pressure-volume points to characterize the diastolic PVR is more clinically feasible when methods other than the conductance catheter are used to measure volume. A limited number of pressure-volume points can approximate the passive diastolic PVR obtained from the MB method, although not as accurately as when more data points are available. The reason for the discrepancy in the three-point RC-SB and MB methods probably lies in the variability introduced by forcing a limited number of pressure-volume points to a monoexponential equation.

External Forces

The present study confirms the effect that forces extrinsic to the LV have on the LV-filling pressure. The source of these forces is likely an interplay between the pericardium and the right ventricle and interaction between the LV and the right ventricle through the interventricular septum (9). The fact that acute volume overload in the absence of the pericardium did not affect the accuracy of the SB method underscores the central role of the pericardium in manifesting the effects of external forces. In fact, LeWinter and Pavelec (16) demonstrated that the constraining effect of the pericardium in dogs is mostly present during acute but not chronic volume overload, consistent with our findings. Our study did not, however, assess for an interaction between the two ventricles independent of the pericardium (9).

Limitations

Late relaxation in filling hearts may be more rapid than predicted by a monoexponential equation (36). Thus the present method may overcorrect for relaxation in SB analysis. Conversely, other studies have shown that relaxation may be more prolonged in filling than in nonfilling hearts and that a monoexponential decay is an appropriate approximation of the actual relaxation (23). The use of a monoexponential equation...
without an asymptote may not be the ideal model to describe the PVR (6, 11). Moreover, extrapolation of relaxation from the isovolumic period overlooks the fact that the myocardially active force decay changes with changing ventricular volume once the mitral valve opens (32). This fact may have contributed to the small, but statistically significant, difference between the RC-SB and MB methods in the volume-overloaded dogs.

All YN and OH dogs had complete relaxation by end diastole; thus the MB method was unlikely to have been affected by relaxation, although with more severe impairment in relaxation the potential for interference with the MB method exists. Other methods may need to be used when measuring the passive properties if very severe relaxation impairment or high heart rates are present.

We used marked rapid volume loading to assess effects of external forces in an open-chest model, and these conditions may exaggerate or underemphasize effects of external forces observed clinically with an intact thoracic cavity. Additionally, we did not assess the SB method in patients with systolic heart failure, and our findings cannot necessarily be extrapolated to dilated hearts with severe systolic and diastolic dysfunction or to patients with significant volume overload.

Clinical studies are also limited by the method used to assess volume. However, the present data provide insight into the validity of these different methods, free from this confounding factor.

Clinical Implications

Several human studies have attempted to define the LV diastolic mechanical abnormalities in some disease conditions, particularly in HFnmEF (14, 21, 37). Further invasive studies are needed to establish the differences in LV diastolic stiffness in different subgroups of patients with HFnmEF, the changes in diastolic performance under different conditions (such as exercise), and the impact of therapies targeting diastolic dysfunction (24). Because the MB method requires acute IVC occlusion that is time consuming, aggressive, and necessitates use of conductance catheter, the SB method can be done by superimposing the LV pressure recording on a single-beat volume assessment obtained, for example, from echocardiography or angiography, which is more practical and clinically applicable. Use of the RC-SB method in patients in whom acute volume overload has been treated and use of appropriate parameters to compare diastolic PVR between groups will facilitate these types of studies.

Conclusions

The present analysis confirms and extends previous theoretical and clinical studies suggesting that SB data, if corrected for the effect of relaxation on diastolic pressures, can substitute for the MB technique in constructing the diastolic PVR in the absence of acute volume expansion. We further illustrate the implications of using β and the LV capacitance for comparing positions of the diastolic PVR between groups.

GRANTS

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REFERENCES


