Stroke Volume Dynamics During Progressive Exercise in Healthy Adolescents

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Understanding cardiac responses to exercise in healthy subjects is important in the evaluation of youth with heart disease. This review article incorporates previously published original research from the authors’ laboratory to examine changes in stroke volume during progressive exercise which are consistent with a model in which circulatory responses are controlled by alterations in the systemic vascular resistance.

Stroke volume dynamics and cardiovascular responses to a progressive upright cycle test were examined in three groups of healthy, untrained adolescent subjects. These indicated a) a progressive decrease in systemic vascular resistance, b) little change in stroke volume after an initial rise related to orthostatic changes in ventricular refilling, c) evidence of a constant or slightly declining left ventricular end diastolic filling pressure, d) and increases in markers of ventricular contractility. These observations are consistent with peripheral (vascular resistance) rather than central (cardiac) control of circulation with exercise. Changes in stroke volume during exercise need to be interpreted in respect to alterations in heart rate and myocardial functional capacity.

From a mathematical perspective, stroke volume is a primary contributor to cardiac output. When multiplied by the heart rate, the volume of blood expelled by the left ventricle per beat defines the circulatory flow (cardiac output) over time expelled by the left ventricle. Enhancement or decrement of stroke volume can therefore be expected to serve as key markers of alterations in cardiac function and circulatory flow (36). For this reason, attention traditionally has been focused on factors responsible for variations of stroke volume as an indicator of cardiac functional capacity in both health and disease.

The set of loading conditions and sympathetic neurologic influences which define the quantity of cardiac stroke volume are well-recognized (13). Stroke volume is augmented by increases in preload (enhanced end-diastolic ventricular volume) via the Frank-Starling mechanism as well as cardiac sympathetic stimulation but is diminished in the face of a rise in after load (increased wall stress, greater peripheral vascular resis-
Changes in stroke volume thus reflect the combined influences of these factors while serving as a prime indicator of the overall effectiveness of the cardiac pump.

This traditional model of the role of stroke volume in reflecting the role of the heart as the primary controller of circulatory flow is not, however, consistent with the cardiovascular responses observed during endurance exercise (37). Data initially obtained from studies in animals and humans in the 1950s indicated that facilitation and control of blood flow during such exercise is related to the role of peripheral rather than central (i.e., cardiac) factors, most specifically the decline in peripheral vascular resistance occurring within the exercising muscle (17,47). By this concept, too, local vasodilatory factors within muscle conveniently link circulatory flow rate to its augmented metabolic demands during exercise (9).

This model of circulatory control during exercise is an expression of Poiseuille’s Law, $Q \sim P/R$, whereby the circulatory flow rate ($Q$) is inversely related to peripheral resistance ($R$) but directly to arterial pressure ($P$), which is maintained by heart function. As Guyton concluded, “The heart has relatively little effect on the normal regulation of cardiac output….The primary cause of augmented cardiac output is believed to be the local vasodilatation in the skeletal muscle” (17).

The dynamics of heart rate and stroke volume during exercise-induced increases in circulatory flow in this scenario are defined by the volume of systemic venous return. By this model the stroke volume remains constant during increased exercise intensity as blood return to the heart increases, a reflection of increased heart rate that matches the venous return and maintains a constant left ventricular filling volume (preload). An increase in ventricular contractility during exercise from sympathetic stimulation and fall in peripheral vascular resistance increase myocardial contractile function, which serves to maintain a constant stroke volume as the ejection time shortens.

In this scenario outlined above, stroke volume during exercise remains defined by the same traditional loading and stimulant factors as in the resting state. However, in the peripheral model of circulatory responses to exercise the “meaning” of the stroke volume changes, for the volume expelled per beat is not a functional determinant of circulatory flow but rather a reflection of changes in heart rate and myocardial contractility as cardiac output rises as a consequence of the fall in peripheral vascular resistance.

Contemporary studies have supported this concept, as reviewed by Rowland in 2008 (38). More recently we have examined changes in stroke volume during progressive cycle exercise in young people in a series of three studies using Doppler echocardiographic techniques. In this report we use the findings in these reports to examine new evidence in respect to the peripheral model. These previously-published investigations provide additional information to support this concept, specifically with data indicating a) the stability of left ventricular filling pressure and b) augmented inotropic function (as indicated by tissue Doppler imaging) with increasing exercise intensities. According to the peripheral model, a fall in systemic vascular resistance with progressive exercise in these studies should be expected to be accompanied by steady increases heart rate, cardiac output, and inotropic function with little change in stroke volume or left ventricular preload.

It is important to recognize that this report describes findings during exercise conducted in normothermic ambient conditions in healthy adolescent subjects who were nonobese and physically active but athletically untrained. In other groups (particularly the elderly, highly-trained athletes, and patients with heart disease) stroke volume responses to exercise may differ (16,35).
Methods

The three studies included in this report were all conducted in the Pediatric Exercise Laboratory at Liverpool Hope University from 2008 to 2010, using similar testing protocols. Study A involved 10 young adolescent males (mean age 15.3 ± 0.5 years), Study B 9 young adolescent females (mean age 15.0 ± 0.6 years), and Study C 14 older adolescent males (mean age 17.9 ± 0.7 years). Findings in these studies have been previously published in investigations of the effect of aerobic fitness on myocardial performance (41), sex differences in myocardial functional response to exercise (46), as well as time-of-day effects on cardiac variables (45). For the purposes of this review, only data on athletically untrained participants in the three studies are presented. These studies were approved by the ethics committee of Liverpool Hope University. Informed consent and assent for participation were obtained from parents and subjects, respectively.

All participants were in good health and taking no medications that would affect cardiovascular function. By self-assessment of level of sexual maturation, participants in studies A and B were in middle stages of puberty, while those in study C were in late puberty or fully mature.

Body composition was assessed by air displacement plethysmography (Bodpod, Life Measurement Incorporated, Concord CA). Before testing a screening echocardiogram was performed to rule out cardiac anatomic or functional abnormalities.

Participants cycled in the upright position with a progressive protocol of 3-min work stages on an electronically braked cycle ergometer (Excalibur Sport 925900; Lode, Groningen, the Netherlands). Initial and incremental loads were 35 Watts for studies A and B and 40 Watts for study C. Pedaling rate was 60 rpm. Participants cycled to the point of exhaustion, with verbal support, defined as the point when the specified cadence could not be maintained.

Gas exchange values were obtained using standard open circuit techniques. Maximal oxygen uptake was defined as the mean of the two highest 20-s average values recorded during the final minute of exercise. A true exhaustive effort was considered to have been achieved if respiratory exchange ratio over 1.00 and/or peak heart rate exceeding 180 bpm (study A and B) or 175 bpm (study C) in conjunction with subjective evidence of fatigue (hyperpnea, sweating, discomfort).

Heart rate was measured electrocardiographically. Stroke volume was estimated by standard Doppler echocardiographic techniques (44). Velocity of blood flow in the ascending aorta was recorded by a 1.9 MHz transducer directed inferiorly from the suprasternal notch with a sweep speed of 100 mm per second. The integral of the resultant velocity-time curves (VTI) was measured off-line. The VTI values of the 3–5 curves with consistent highest values were averaged and multiplied by the cross-sectional area at the level of the aortic valve leaflets to obtain estimated stroke volume. This area was calculated from the diameter measured between the hinge points of the fully-open aortic valve via 2-dimensional echocardiography (parasternal long axis view) with the subject at rest sitting on the cycle ergometer. The aortic valve ring was considered to be circular in this position, and changes in diameter during the ejection period with exercise were assumed to be minimal. Acceptable test-retest reproducibility and validity of this technique for assessing stroke volume during maximal exercise have been described (44).
Blood pressure was measured in the left arm by the auscultatory technique. Diastolic pressure (MAP) was calculated as 1/3 (systolic-diastolic) + diastolic pressure. Cardiac output (Q) was calculated as the product of stroke volume and heart rate, and systemic vascular resistance was computed as MAP/Q. Cardiac output and stroke volume were related to body surface area as the cardiac index and stroke index, respectively.

Flow velocity across the mitral valve in early diastole (E wave) was estimated by pulse wave Doppler interrogation at the tips of the open valve leaflets in the apical four-chamber view. Peak values were calculated as the mean of the 3–5 consistently highest velocities. Late inflow velocity (mitral A wave) was not considered in these studies, since this wave merged with the E wave at low exercise intensities. Values of mitral E were interpreted as reflecting the pressure gradient between “upstream” factors (left atrial volume, pressure) and those “downstream” (left ventricular relaxation properties) during diastole (43,57).

Left ventricular longitudinal velocities were recorded by pulse wave tissue Doppler imaging (TDI) at the lateral aspect of the mitral valve annulus in the apical four-chamber view. Peak TDI-S and TDI-E’ velocities were determined as the mean of the 3–5 consistently highest values and interpreted as longitudinal velocities in systole and early diastole, respectively. (TDI-S was not recorded in study A.) These measurements were made while attempting to maintain alignment between the transducer beam and the vertical axis of the heart. All determinations were made during spontaneous respirations. TDI-S and TDI-E’ were considered as markers of systolic (inotropic) and diastolic (myocardial relaxation) function, respectively (34,49). Values of E/E’ were considered indicative of left ventricular filling pressure (28).

The series of measurements of blood pressure, heart rate, VTI, mitral E, and TDI was performed at rest, starting at 1:30 in each work stage, and during the final minute of exercise. During the latter determination participants were requested to maintain an upright posture and avoid exaggerated body movements but were not otherwise constrained.

Systolic ejection time was obtained from the VTI curve. Systolic function was estimated by the systolic ejection rate (calculated as the stroke volume divided by ejection time), peak aortic velocity, and peak value of tissue Doppler-S (6,27). Values are expressed as mean±SD. Unless otherwise noted, increases with respect to exercise intensity were statistically significant for all measures.

Results and Discussion

Percent body fat for participants in studies A, B, and C were 16.0 ± 5.4%, 20.1±5.8%, and 15.3 ± 3.4%, respectively. Screening echocardiograms were normal in every subject. All subjects satisfied criteria for an exhaustive exercise effort. Physiological variables measured preexercise and at maximal exercise in the three studies are outlined in Table 1. Cardiac output rose by factors of 2.6, 3.1, and 3.4. Calculated total peripheral vascular resistance between rest and maximal exercise fell by -51% in study A and by -68% in study B. (Because of technical difficulties blood pressure was not recorded in study C).
Table 1  Cardiovascular Variables With Exercise in the Three Study Groups. Values Are Mean (Standard Deviation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study A</th>
<th>Study B</th>
<th>Study C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2}$max (ml kg$^{-1}$ min$^{-1}$)</td>
<td>44.4(6.6)</td>
<td>36.0(5.1)</td>
<td>44.0(5.0)</td>
</tr>
<tr>
<td>Heart rate max (bpm)</td>
<td>195(11)</td>
<td>191(9)</td>
<td>190(11)</td>
</tr>
<tr>
<td>Respiratory exchange ratio max</td>
<td>1.12(0.05)</td>
<td>1.07(0.07)</td>
<td>1.26(0.07)</td>
</tr>
<tr>
<td>Systemic vascular resistance (units)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>16.6(6.1)</td>
<td>23.0(6.9)</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>8.1(0.2)</td>
<td>7.4(1.5)</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (L min$^{-1}$ m$^{-2}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>3.52(1.08)</td>
<td>2.55(0.72)</td>
<td>2.96(0.53)</td>
</tr>
<tr>
<td>Max</td>
<td>9.02(2.05)</td>
<td>7.80(1.03)</td>
<td>10.13(1.18)</td>
</tr>
<tr>
<td>Stroke index (ml m$^{-2}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>42(10)</td>
<td>33(6)</td>
<td>42(7)</td>
</tr>
<tr>
<td>Max</td>
<td>46(10)</td>
<td>41(4)</td>
<td>54(6)</td>
</tr>
<tr>
<td>Systolic ejection time (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>266(37)</td>
<td>251(17)</td>
<td>243(18)</td>
</tr>
<tr>
<td>Max</td>
<td>198(10)</td>
<td>170(7)</td>
<td>158(13)</td>
</tr>
<tr>
<td>Systolic ejection rate (ml s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>0.158(0.034)</td>
<td>0.204(0.042)</td>
<td>0.326(0.053)</td>
</tr>
<tr>
<td>Max</td>
<td>0.234(0.051)</td>
<td>0.368(0.060)</td>
<td>0.654(0.086)</td>
</tr>
<tr>
<td>Peak aortic velocity (ml s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>136(23)</td>
<td>108(16)</td>
<td>118(17)</td>
</tr>
<tr>
<td>Max</td>
<td>208(45)</td>
<td>196(12)</td>
<td>232(27)</td>
</tr>
<tr>
<td>Mitral E (cm s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>72(9)</td>
<td>75(17)</td>
<td>64(16)</td>
</tr>
<tr>
<td>Max</td>
<td>149(23)</td>
<td>155(18)</td>
<td>149(14)</td>
</tr>
<tr>
<td>Tissue Doppler S (cm s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>7.5(1.6)</td>
<td>8.4(2.3)</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>18.6(2.6)</td>
<td>18.3(1.9)</td>
<td></td>
</tr>
<tr>
<td>Tissue Doppler E’ (cm s$^{-1}$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>12.0(2.0)</td>
<td>11.8(2.0)</td>
<td>9.1(2.9)</td>
</tr>
<tr>
<td>Max</td>
<td>28.0(5.0)</td>
<td>26.8(2.7)</td>
<td>24.9(2.4)</td>
</tr>
<tr>
<td>E/E’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>6.11(1.5)</td>
<td>6.55(2.1)</td>
<td>7.63(1.3)</td>
</tr>
<tr>
<td>Max</td>
<td>5.39(0.93)</td>
<td>5.81(0.62)</td>
<td>6.08(0.97)</td>
</tr>
</tbody>
</table>
Pattern of Changes in Stroke Volume

Figure 1 indicates the pattern of stroke index with increasing cycle work to exhaustion in the three studies. All show the same configuration, with an initial rise (of approximately 25%), followed by little change above a low-moderate work load.

This pattern of stroke volume response to upright exercise is consistent with previous reports. In fact, an initial rise with subsequent little change at higher work intensities (a so-called “plateau”) is one of the most consistently observed findings in cardiac exercise physiology. Supporting its validity, this pattern of stroke volume response to upright exercise has been described utilizing multiple techniques in a wide age range of subjects from prepubertal to middle-age. These have included indirect Fick (CO2 rebreathing; 2), direct Fick (53), thermodilution (20), thoracic bioimpedance (5), dye dilution [10,11,19], radionuclide angiography (32), and Doppler echocardiography (26,56).

It has been considered that this initial rise in stroke volume observed during the initial phases of upright exercise reflects the mobilization of blood sequestered in the lower extremities by gravity when assuming the upright or seated position (3,48). Blood volume in the legs increases by 500–1,000 ml when an adult becomes upright, a response which reduces central volume and consequently left ventricular preload. As a result, cardiac output and stroke volume fall by 20–40%. At the start of upright exercise, the pumping action of the contracting skeletal muscles in the leg reverse this effect. Blood is returned to the central volume, which augments left ventricular preload, and via a Frank-Starling mechanism effects a rise in stroke volume (55).

Early studies provided an experimental underpinning for this mechanism. Pollack and Wood reported that during the first steps of walking, venous pressure at the ankle fell from 100 to approximately 40 mm Hg (33). Similar declines were documented by Stick et al. (52) and Stegall (50) during treadmill walking.

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**Figure 1** — Stroke index responses during upright progressive cycle exercise in the three study groups. Dashed lines connect to average maximal values.
Evidence supporting this concept is provided by stroke volume values at supine rest followed by upright exercise demonstrated in Study C. As indicated in Figure 2, average stroke volume fell by 25% when moving to the sitting position (with dependent legs) on the cycle ergometer from supine rest. With the onset of exercise, stroke volume rose to approximate that recorded in the supine position, with little further change as work intensity rose.

As expected, then, most studies have revealed no initial rise in stroke volume when progressive cycle exercise is performed in the supine position (3,22,42,51). However, some have reported initial increases during both supine and upright exercise, although with a greater magnitude of rise in the latter (32,54).

A similar “flat” stroke volume response to progressive exercise is observed in other conditions in which the influence of gravity is eliminated. No initial rise in stroke volume has been reported with prone simulated swimming (40), astronauts exercising in the microgravity of outer space (1), arm exercise (24), and upright exercise while submerged in a pool, where the hydrostatic pressure gradient of the surrounding water displaces blood cephalad away from the lower extremities (7).

These data provide compelling evidence that the early rise of stroke volume during upright exercise reflects simply a “refilling” phenomenon, a manifestation of increased left ventricular diastolic filling (Frank-Starling mechanism). Beyond this response, which is related to orthostatic alterations in central blood volume, stroke volume changes little with progressive exercise.

**Alterations in Ventricular Filling (Preload)**

In the three present studies, values of mitral E peak velocity rose 2.1-, 2.1-, and 2.3-fold with increasing work intensity, indicating a rise in the left atrial-left ventricular pressure gradient in the early portion of ventricular diastole which drives ventricular filling. Concomitantly, TDI-E’ rose by factors of 2.3, 2.3, and 2.7, indicative
of augmented diastolic function (relaxation properties, elastic recoil) of the left ventricle. The ratio of E/E’, however, did not change significantly and in all cases demonstrated a slight gradual decline (Figure 3). E/E’ is considered as an indicator of “upstream” left atrial pressure and reflects left ventricular filling pressure. This pattern of E/E’, then, is consistent with a stable (or slightly decreasing) left ventricular end diastolic volume, or preload, in the course of progressive exercise.

These findings are consistent with reports by two-dimensional echocardiography [15,31,39] and radionuclide ventriculography [20,21,29,58] that left ventricular end diastolic dimension remains unchanged or gradually declines with increasing exercise intensity. In these studies of responses to upright exercise, this pattern was often preceded by a slight rise at onset of exercise, consistent with the process of orthostatic-related ventricular refilling noted above.

This stable filling volume occurs concomitantly with a 3-fourfold rise in systemic venous return to the heart. To maintain a constant left ventricular filling volume per beat, this influx of blood flow must be de facto tightly coupled to a corresponding rise in heart rate. The Bainbridge reflex, by which a rise in atrial pressure or volume triggers a sympathetic reflex that increases sinus node firing rate, offers a means by which this might be accomplished. The true existence of this reflex, first proposed over a century ago, has been surrounded by controversy, but its function has been clearly demonstrated in both humans and subhuman primates (4,18,30). It can be considered the best mechanistic explanation for the close match between heart rate and systemic venous return by which the per-beat ventricular filling volume remains constant during progressive exercise. Alternatively, however, Clausen suggested that the close link of heart rate to systemic venous return to the heart might be explained by sympathetic reflexes originating in the contracting skeletal muscle (8).

This information provides evidence that progressive exercise in the upright position is initiated by an early increase in ventricular filling from mobilization of dependant blood in the lower extremities. Following this, ventricular preload remains constant or declines slightly, the consequence of a rise in heart rate to match

![Figure 3](image-url) — Values for E/E’ in the three study groups with progressive upright cycle exercise.
increases in systemic venous return. It appears, then, that this mechanism “defends” left ventricular end diastolic size as exercise intensity increases, for failure of heart rate to increase appropriately would result in progressive left ventricular dilatation. This would result in a disadvantageous increase in left ventricular wall tension and diminished mechanical efficiency as predicted by the law of Laplace (23).

Myocardial Inotropic Responses

As exercise intensity increases, myocardial systolic function is enhanced, expressed as a greater force and velocity of contraction. This results in a progressive shortening of the systolic ejection time, as well as an increased ventricular shortening fraction or ejection fraction as end systolic dimension decreases.

This enhanced myocardial contractility is documented in our three studies by parallel increases in markers of systolic function with increasing work. Systolic ejection rate, TDI-S, and peak aortic velocity all rose approximately twofold. At the same time, consistent with the research literature (e.g., Higgenbotham et al. (20)), systolic ejection time per beat decreased by 25%, 32%, and 35% in the three studies.

Previous studies have indicated that while progressive exercise is accompanied by a relatively stable left ventricular end diastolic dimension, the end systolic dimension progressively decreases (31,39). This results in an increase in shortening fraction (the difference between left ventricular end diastolic dimension and systolic dimension divided by diastolic dimension, multiplied by 100), typically from 30% at rest to 50% at maximal exercise (17,31,39). The ventricular ejection fraction, the three-dimensional counterpart of the shortening fraction estimated by nuclear angiography, generally rises by 10–15% during a progressive exercise test (12,58).

Several factors may potentially contribute to this rise in inotropic function with progressive exercise: a) decrease in afterload (with stable left ventricular size, indicated by the fall in systemic vascular resistance), b) direct sympathetic nervous myocardial stimulation, and c) the increasing heart rate (the force-frequency phenomenon). Each of these influences can act independently to augment myocardial contractility and shorten ejection time; thus, identifying their relative contributions to alterations in myocardial contractile function with exercise is problematic (6,14,25).

These observations serve to create an apparent paradox. It is clearly documented that the ventricles empty more completely (as a consequence of enhanced myocardial contractility) as work load increases, yet the volume expelled per beat (stroke volume) remains stable (after an initial refilling phase). This quandary is resolved by recognizing that the enhanced contractility serves to eject the same volume of blood during a progressively shortening ejection time. The effect of augmented myocardial contractility with progressive exercise, therefore, is to maintain, rather than increase, stroke volume in the face of an increasingly abbreviated ejection period.

Summary

The response of the cardiovascular system in providing circulatory support for endurance exercise involves a remarkably fine-tuned synchrony of interrelating variables. The exercise studies described in this report, combined with information from previous investigations, indicate that, after early postural-related ventricular refilling, upright progressive cycle exercise performed by healthy, young, untrained
individuals is accompanied by a) a steady fall in systemic vascular resistance, b) little change in stroke volume, c) stable or slightly decreasing ventricular preload, and d) progressive increases in markers of myocardial systolic function. This constellation of findings is consistent with a peripheral model of circulatory control during exercise, modulated by alterations in systemic arteriolar conductance, in which cardiac dynamics are dictated by the volume of systemic venous return. In this model, as Clausen emphasized, “the vasodilation in muscle that is locally adjusted to the work load may be considered the fundamental determinant of cardiac output during exercise” (8).

The extraordinary complexity of the cardiovascular responses to endurance exercise precludes an over-simplistic reductionist approach. The myriad components of this response must all function in harmony, and in accordance with the dictates of “symmorphosis,” the capacity of no single component should exceed that of the entire system. Still, the experimental data obtained from the studies presented in this report support the concept that peripheral control (i.e., alterations in muscular arteriolar conductance) serves as the primary factor for instigating and regulating level of circulatory blood flow during exercise in healthy individuals. Whether this factor, or others, are responsible for defining the limits of circulatory responses to exercise remains a critical but unanswered question.

This information does indicate that during endurance exercise, stroke volume should be considered as a secondary, resultant variable influenced by a) the relationship between systemic venous return to the heart and the heart rate, and b) increases in systolic and diastolic myocardial function. Any changes in stroke volume observed during exercise therefore need to be interpreted in the context of these modifying variables.

Acknowledgments

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References


