In Vitro Perfusion Studies of Resistance Artery Function in Genetic Hypertension

Brendan J. Falloon, Stuart J. Bund, Jonathan R. Tulip, Anthony M. Heagerty

To examine the function of resistance-sized arteries in hypertension under in vitro conditions that approximate in vivo conditions as much as possible, we mounted segments of second-order mesenteric resistance arteries from spontaneously hypertensive rats (SHR) and Wistar-Kyoto normotensive control rats aged 12 to 13 weeks in a perfusion myograph and exposed them to conditions of constant flow and pressure. The endothelial integrity was validated both functionally and histologically. Vascular sensitivity to norepinephrine was examined when the hormone was applied either intraluminally or extraluminally and before and after removal of the endothelium. Both endothelium-dependent and -independent dilatation was assessed by the intraluminal application of acetylcholine and sodium nitroprusside, respectively. Sodium nitroprusside was applied to arteries after endothelium removal. Arterial responses were measured by changes in intraluminal diameter recorded with a video camera and imaging system. Vessels from SHR demonstrated depressed endothelium-dependent relaxation but similar endothelium-independent relaxation and greater sensitivity to norepinephrine with both intraluminal and extraluminal application. Removal of the endothelium abolished the differences in sensitivity to norepinephrine between the two strains. The results demonstrate that resistance arteries from SHR when examined under in vitro perfusion display enhanced sensitivity to norepinephrine due to depressed endothelium-dependent dilatation, and the data suggest that functional modifications in the endothelium may play an important role in hypertensive vascular disease. (Hypertension. 1993;22:486-495.)

KEY WORDS • endothelium • norepinephrine • acetylcholine • nitroprusside • vascular resistance • hypertension, genetic • rats, inbred SHR

The endothelium plays a potentially important role in modulating responses of underlying smooth muscle. This can be attributed to its unique position in the vasculature: it lines all blood vessels, thus separating circulating blood from vascular smooth muscle cells. Therefore, the endothelium is likely to be a promoter and target of hypertension. However, its role in regulating vascular tone has only recently become apparent, following the work of Furchgott and Zawadzki. Subsequently, numerous reports have described the endothelial dependence of a large number of vasodilators and the antagonistic effect of the endothelium on the action of several vasoconstrictors. In hypertension there is evidence for changes in vascular responsiveness, such as increased reactivity to vasoconstrictors and reduced net relaxation responses to the endothelium-dependent dilator acetylcholine. Also, there is increasing evidence that the sympathetic nervous system plays a role in the development and maintenance of hypertension, and neuronal amine uptake appears to be greater in the spontaneously hypertensive rat (SHR) and human essential hypertension. Changes in vascular responsiveness have been ascribed to modifications in the arterial wall such as medial hypertrophy and hyperplasia, which are the adaptive hallmarks of hypertension and which result in medial encroachment on the lumen. However, functional alterations may have an additional important role. In particular, endothelial dysfunction, resulting in impaired endothelium-dependent relaxation, may contribute to an increased peripheral resistance.

A number of problems have emerged with respect to the study of vascular tissues in hypertension. In SHR, many studies examined functional activity in the aorta or tail artery using segments of vessel mounted as ring preparations on wires. Studies of smaller arteries, resistance arteries, became important when it was realized that they were hemodynamically more important and possessed intrinsically different properties from vessels upstream. The function of these arteries can be investigated with a myograph. This technique, which is essentially a ring preparation, allows small precapillary arteries (100 to 500 μm), which contribute significantly to peripheral vascular resistance, to be studied under precise and standardized conditions. However, such in vitro techniques distort the arterial segment, exclude the influence of fluid flow across the luminal surface, and present most pharmacologically active substances to the adventitial and luminal surfaces simultaneously. More recently, techniques have been developed to extend studies of resistance arteries in vitro; pressure perfusion chambers allow the vessel to be examined under more physiological conditions.
tion, the diameter of the vessel is allowed to change in response to agonists; the endothelium remains untouched in the mounting procedure; the walls of the vessel experience an intraluminal pressure; the vessel assumes a more physiological shape, allowing for both longitudinal distension and reversal of the retraction of dissection; and agonists may be perfused intraluminally or superfused extraluminally. But, perhaps most importantly, vessels can develop intrinsic tone and constrict in response to increases in pressure, thus exhibiting a myogenic response that rarely occurs in ring-mounted preparations. Therefore, a cannulated blood vessel perfused at a regulated intraluminal pressure and flow rate is a superior physiological preparation and may reflect more accurately smooth muscle sensitivity. The purpose of the present study, therefore, was to further investigate the function of resistance arteries in genetic hypertension in the presence of luminal flow and the absence of wires down the lumen. As yet, there is no evidence to suggest that differences in the type of vessel preparation used alter the responses to norepinephrine and acetylcholine.

**Methods**

**Animals**

Fourteen SHR and 14 control Wistar-Kyoto (WKY) rats were obtained from the university stock colonies originally from Charles River (Kent, UK) and maintained on standard rat chow and tap water ad libitum. Male rats 12 to 13 weeks old were studied throughout. Body weight and indirect systolic blood pressure measurements were recorded at least 24 hours but not more than 1 week before rats were used. Systolic blood pressure was measured with the rats under light ether anesthesia using tail-cuff plethysmography. Male rats were killed by stunning followed by cervical dislocation. All procedures were followed in accordance with Home Office guidelines.

**Drugs and Solutions**

All experiments involving isolated resistance arteries were performed using physiological saline solution (PSS) of the following composition (mmol/L): NaCl, 119; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 1.17; NaHCO₃, 25; KH₂PO₄, 1.18; EDTA, 0.026; and glucose, 5.5. Potassium-PSS was PSS with an equimolar replacement of the NaCl with KCl, resulting in a final potassium concentration of 125 mmol/L. All solutions were bubbled with 95% O₂-5% CO₂ to give a pH of 7.4 at 37°C. Norepinephrine (±)arterenol hydrochloride), acetylcholine chloride, and sodium nitroprusside were purchased from Sigma Chemical Co, Poole, UK.

**Flow System**

After stunning and cervical dislocation, the entire mesentery was excised by means of a longitudinal abdominal incision and placed in ice-cold PSS. A 3- to 4-mm segment of the second-order branch of the superior mesenteric artery was dissected out after careful removal of all extraneous adipose tissue. One arterial segment was taken from each rat. The proximal end of the artery was identified by a diagonal cut to facilitate maintenance of the normal directional flow through the vessel after mounting. After dissection, the artery was transferred to the vessel flow chamber containing cold PSS. In the chamber are two glass resistance-matched microcannulas used to perfuse the artery (Fig 1). One cannula is fixed (the distal cannula); the other (the proximal cannula) can be positioned as appropriate. The proximal end of the artery was slipped onto the proximal cannula, and any residual blood in the artery was gently flushed. The distal end of the artery was then slipped onto a cannula and the ends of the vessel secured to the cannulas with cyanoacrylate glue (Locite Superbonder 495, Industrial Fasteners, Leicester, UK) to obtain a watertight seal. The chamber was then washed several times with ice-cold PSS. The glue hardened immediately on contact with the PSS. The axial length was set by viewing the vessel under a dissecting microscope and carefully adjusting its length by positioning the proximal cannula to eliminate any warping or buckle, taking care not to stretch or compress the vessel longitudinally. Approximately 2 to 3 mm of the arterial segment lay between the cannulas. The temperature in the vessel chamber was controlled by a circular heating coil and monitored continuously by a thermistor probe (Ellab, Copenhagen, Denmark) placed through the chamber wall into the bath. The flow chamber was placed onto the stage of an upright microscope (Nikon Labophot, Seescan, Cambridge, UK) with a video camera attached to the viewing tube and connected to an imaging system (Seescan) that allows arterial images to be stored for subsequent measurement of vessel dimensions. The temperature of the vessel environment was slowly raised to 37°C. Vascular flow was initiated with a peristaltic pump. Preheated and pregassed PSS was passed at a constant flow rate through a short length of relatively noncompliant insulated polyethylene tubing.
attached to the proximal cannula. A pressure transducer connected upstream from the proximal cannula allowed measurement of perfusion pressure. Transmural pressure was produced by a PSS column connected downstream from the distal cannula. At the flow rate and cannula size used (200-μm internal diameter), the pressure drop across the inflow cannula was negligible so that intraluminal pressure was effectively equal to the inflow pressure. The level of PSS in the column remained constant. The height of the column when full produced a transmural pressure of 30 mm Hg. Excess PSS overflowed into a reservoir. After transmural pressure and flow had been established, the vessel was checked for leaks. These were identified by a drop in the level of PSS in the column and a reduction in the preset intraluminal pressure. During the equilibration period, the intraluminal pressure of the vessel was raised to 60 and 90 mm Hg and the proximal cannula adjusted until the artery was unbuckled and the walls were parallel. In the absence of leaks, the vessel was equilibrated for at least 1 hour. Although all of the arterial segment was viable, an optically clean portion of the magnified vessel was chosen, usually close to the midpoint to avoid the cannulas entering the field of vision and to eliminate any influence the cannulated sections may have had on the arterial responses. Medial thickness and internal lumen diameter were measured at 30 mm Hg with the artery fully relaxed in PSS perfusate and superfusate. Arteries did not develop intrinsic tone even at higher transmural pressures of 60 and 90 mm Hg. Myogenic tone has been previously been documented. To overcome this, we took all vessel measurements at six equidistant points along the length of the vessel displayed on the screen, and the mean values were calculated.

Between successive increasing concentrations of norepinephrine, arteries were washed with PSS and allowed to relax fully. Application of extraluminal norepinephrine concentrations was achieved by draining the chamber followed by addition of PSS containing the required concentration of norepinephrine; intraluminal norepinephrine concentration changes were accomplished by replacement of the perfusate reservoir with one containing the required norepinephrine concentration. Tissues were washed between intraluminal and extraluminal drug application with PSS and rested for 15 to 20 minutes before subsequent concentration-response relations were determined. The order in which the intraluminal and extraluminal experiments were carried out was randomized. Contractions were calculated.

**Vascular Reactivity**

After the equilibration period, vessels were activated by perfusion with 10 μmol/L norepinephrine in KPSS (NEK) and then with 10 μmol/L norepinephrine in PSS, and then again with NEK to determine tissue viability (Fig 2). An artery was considered viable if it contracted to more than 60% of its resting lumen diameter with NEK. Any artery that did not fulfill this criterion was discarded and another vessel mounted. A steady contraction was maintained for 1 minute for each activation. Between each stimulation, the vessel was perfused with PSS and allowed to relax fully. The maximum contraction was produced by either the second or third application of NEK, and the greater response was taken as maximum for each artery. Norepinephrine concentration-response relations were obtained for each artery by intraluminal and extraluminal application (5 x 10⁻⁷ to 10⁻⁴ mol/L) in both the presence and absence of the endothelium. Pilot experiments showed no time-dependent shift in norepinephrine sensitivity in either SHR or WKY rats (Fig 3). The constriction to both intraluminal and extraluminal norepinephrine in WKY vessels was consistent along the length of the segment. However, in SHR some vessels at submaximal concentrations exhibited unequal constriction, which has previously been documented. To overcome this, we took all vessel measurements at six equidistant points along the length of the vessel displayed on the screen, and the mean values were calculated.

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stricted with norepinephrine as described previously for endothelium to determine the direct effect of nitric oxide on the smooth muscle cells. Arteries were preconstricted with norepinephrine to a particular concentration of norepinephrine applied to the vessel, and LD3 is the smallest lumen diameter induced by norepinephrine and represents the maximum contraction.

Maximum contractions were expressed as the greatest percentage decrease in lumen diameter and calculated from the expression

\[
\text{% Maximum contraction} = \frac{LD1 - LD2}{LD1 - LD3} \times 100
\]

where LD1 is the lumen diameter when the artery is fully relaxed, LD2 is the lumen diameter achieved by a particular concentration of norepinephrine in the absence of the endothelial layer, and LD3 is the lumen diameter when the artery is fully relaxed.

Endothelium removal was then accomplished by passing an air bubble through the lumen of the vessel using a modification of the protocol of Ralevic et al.25 and was verified by the loss of acetylcholine-induced relaxation (10^{-9} to 10^{-5} mol/L) after the reaction of the arterial segment under study for less than 1 second. Removal was also confirmed by direct observation of the intimal surface by electron microscopy. After endothelium removal, intraluminal and extraluminal application of norepinephrine was repeated in a random fashion.

In a further series of experiments, we investigated endothelium-independent relaxation using sodium nitroprusside (10^{-9} to 10^{-4} mol/L) after the removal of the endothelium to determine the direct effect of nitric oxide on the smooth muscle cells. Arteries were preconstricted with norepinephrine as described previously for acetylcholine, and the relaxation response was expressed similarly.

**Histology**

After the reactivity experiments, arteries were prepared for histological examination. Vessels were incubated in calcium-free PSS containing 0.1 mmol/L EGTA at 37°C to ensure complete relaxation then fixed in 4% cacodylate-buffered glutaraldehyde at a transmural pressure of 30 mm Hg. Arteries were removed from the cunnels, treated with 1% osmium tetroxide, and embedded in Embed 812 resin (Bio-Rad). Longitudinal sections 100 nm thick were cut and counterstained with uranyl acetate and Reynolds lead citrate. Sections were examined with electron microscopy for the absence of the endothelial layer.

**Statistical Analyses**

Statistical evaluation was performed with repeated-measures analysis of variance on both the concentration-response curves and ED_{50} values. The ED_{50} value was the concentration of norepinephrine or acetylcholine required to elicit half-maximal contraction or relaxation, respectively, and was calculated for each experiment separately. Sensitivity is expressed as pD_{2} values, which were calculated as -log (ED_{50}) molar. The statistical distributions of the measures of analyses were evaluated fully. All variables were found to follow approximate normal distributions, so all data were analyzed untransformed. Differences identified by the analyses of variance were examined in detail using the Tukey multiple comparison test. Student’s unpaired t-test was used to compare indirect systolic blood pressures, body weights, media thickness, lumen diameters, and the ratios of media thickness to lumen diameter. A paired t-test was used to compare 10^{-9} and 10^{-5} mol/L acetylcholine responses in both SHR and pooled data from SHR and WKY rats with intact endothelium. Statistical significance was set at the 5% level. Data are given as mean±SEM.

**Results**

Fourteen arteries from both WKY rats and SHR were used in this study. Indirect systolic blood pressures were significantly higher in SHR compared with WKY rats (166.0±1.9 and 117.6±1.3 mm Hg, respectively; P<.001). SHR body weights were also greater than those of WKY rats (303.1±2.1 and 295.1±1.4 g, respectively; P<.001). The morphological measurements of SHR and WKY mesenteric arteries are shown in Table 1. Media thickness in SHR was significantly greater than that of age-matched WKY rats, whereas lumen diameters were significantly less in SHR than WKY rats when...
arteries were fully relaxed in perfusate and superfusate. This resulted in an overall increase in the ratio of media thickness to lumen diameter in SHR arteries. These data are similar to those we have previously reported in studies with wire-mounted preparations.33

Norepinephrine-Mediated Contractions

In mesenteric resistance arteries with endothelium, SHR arteries were more sensitive than WKY arteries with both intraluminal (P<.01) and extraluminal (P<.05) application of norepinephrine (Fig 4). After endothelium removal, the contractions evoked by norepinephrine were comparable in both SHR and WKY arteries irrespective of the route of application (Fig 5). The sensitivities to norepinephrine expressed as pD₂ values are shown in Table 2.

Endothelium removal did not influence resting lumen diameters of either strain (WKY: 302.7±3.9 and 302.3±4.1 µm, respectively; SHR: 282.7±5.8 and 282.3±5.7 µm, respectively). The contractions evoked by NEK before and after endothelium removal did not differ either in WKY rats (69.2±1.1% and 69.4±1.1% decrease in intraluminal diameter, respectively) or in SHR (70.8±0.4% and 71.1±0.3%, respectively). The passage of an air bubble through the lumen removed the endothelium effectively, with preservation of both the basal membrane and the underlying internal elastic lamina (Fig 6). Thus, the histological evidence coupled with the observation that contractile responses to NEK were unaffected demonstrates that passage of an air bubble though the lumen is an efficient method for endothelium removal, with no loss of smooth muscle function.

Acetylcholine-Mediated Relaxation

Acetylcholine produced a concentration-dependent relaxation of constricted resistance artery segments from both SHR and WKY mature rats. However, the SHR arteries displayed attenuated relaxations, and at 10⁻⁵ mol/L acetylcholine, SHR arteries partially reconstituted (Fig 7) (see Table 2 for pD₂ values). The maximal relaxation response was greater in WKY rats than SHR (99.2±0.4% and 83.5±2.6%, respectively; P<.01). After removal of the endothelium, relaxation to acetylcholine was absent in arteries preconstricted with norepinephrine (Fig 8), and no further constriction was observed.

Sodium Nitroprusside-Mediated Relaxations

In the absence of the endothelium, intraluminal application of sodium nitroprusside produced a concentration-dependent relaxation of resistance artery segments preconstricted with norepinephrine from both SHR and WKY rats (Fig 9). The responses were comparable between the two strains (see Table 2 for pD₂ values). The maximal relaxation response was 79.9±3.2% in WKY rats and 83.4±5.5% in SHR (NS).

Discussion

In the present study, contractile and dilator responses of mesenteric resistance arteries were investigated with a pressurized vessel system that allows the arterial wall to experience a true transmural pressure and a more physiological shape. In addition, the endothelium remains untouched during the mounting procedure.

The structural measurements produced show similar results to those obtained in wire and other preparations.
in which mesenteric arteries from SHR and WKY rats have been pressurized and perfused\(^{25}\) or cannulated and pressurized\(^{34}\), a greater wall-to-lumen ratio in the SHR resistance arteries is demonstrated.

The present study demonstrates that under these more physiological conditions there is defective endothelium-dependent relaxation in response to acetylcholine in the mesenteric resistance arteries of adult SHR. In addition, the sensitivity of the SHR arteries to norepinephrine is increased with both intraluminal and extraluminal application of the catecholamine in the presence of the endothelium compared with arteries from WKY rats. However, after endothelium removal, SHR and WKY arteries were equally sensitive to norepinephrine. This indicates that the results are not an artifact of which side the norepinephrine is applied and shows that the endothelium influences the norepinephrine response significantly regardless of the application site.

Therefore, the endothelium would appear to play a pivotal role in the increased norepinephrine sensitivity in the SHR, possibly by means of a depressed release of endothelium-derived relaxing factor (EDRF) or the release of a less potent EDRF. Alternatively, the vascular smooth muscle cells of the SHR may be less sensitive to EDRF. Previous work has demonstrated that the endothelium has a reduced inhibitory effect on the contraction induced by serotonin in mesenteric resistance arteries from SHR compared with those from WKY rats.\(^{35}\) With ring preparations, it has been reported that SHR resistance arteries are more sensitive to norepinephrine than WKY arteries only in the presence of cocaine to inhibit neuronal amine uptake\(^{12,15}\) or after denervation.\(^{18,36}\) This led to the conclusion that there is an increased smooth muscle cell sensitivity to norepinephrine in the SHR that is normally masked by a greater neuronal amine uptake. The data from the present study suggest that defective endothelial function may also contribute substantially to the enhanced arterial norepinephrine sensitivity in the SHR. Because no attempt was made to inhibit neuronal amine uptake in the present study, it could be possible that there was an enhanced smooth muscle norepinephrine sensitivity in the absence of the endothelium but which was masked by an enhanced neuronal amine uptake. In this study we were purely examining the sensitivity to exogenous norepinephrine and how the endothelium influences these responses; i.e., vascular norepinephrine response could be a net result of vascular smooth muscle sensitivity, the influence of neuronal amine uptake, and endothelial function. Further experiments in the presence of cocaine are required to address this question. Differences in shear force generated by different levels of vasoconstriction at the same rate of volume flow may also contribute to the endothelium modulation of norepinephrine sensitivity between SHR and WKY rats.

To our knowledge, currently there are no studies that compare directly intraluminal and extraluminal norepinephrine sensitivity between SHR and WKY rats in perfused pressurized resistance arteries, although the role of the endothelium in the norepinephrine response has been investigated. Dohi et al\(^ {22}\) demonstrated a greater shift in sensitivity on endothelium removal in WKY, which is in agreement with our findings. WKY arteries were less sensitive than SHR arteries in our study in the presence of the endothelium, whereas norepinephrine sensitivity was not significantly different from that in SHR arteries after endothelium removal. This indicates that there is a greater shift in the WKY artery. However, Dohi et al did not directly address interstrain comparisons. They reported a similar sensitivity in SHR and WKY rats with extraluminal norepinephrine application but did not report the sensitivity of the two strains with intraluminal application. Differences in our data could be a consequence of methodological differences, for example, flow rate or the genetic backgrounds of the rats. It has become clear that rat genotypes vary according to source.\(^{33,38}\) Arteries from normotensive rats showed a continuous relaxation response to intraluminally applied acetylcholine, whereas the responses in those from hypertensive rats were significantly reduced and, at the highest concentration used (10\(^{-5}\) mol/L), SHR arteries reconstituted. This effect was endothelium mediated, because after removal of the endothelium acetylcholine did not elicit further constriction in preconstricted arteries of SHR. This indicates that the endothelium of SHR initiates a contraction in response to acetylcholine. Other recent studies using perfused pressurized resistance arteries have shown decreased acetylcholine-induced vasodilation in these vessels,\(^{24,25}\) confirming the observations in a wire-mounted ring preparation.\(^ {39}\) This impairment of relaxation is of particular importance in established hypertension, because attenuated endothelium-dependent relaxation may play a part in the elevated peripheral resistance by augmenting or facilitating contraction, possibly by release of endothelium-derived contracting factors.\(^ {40}\) The loss of endothelium-dependent relaxation

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### Table 2. \(pD_2\) Values for Sensitivity to Norepinephrine, Acetylcholine, and Sodium Nitroprusside

<table>
<thead>
<tr>
<th>Agonist</th>
<th>WKY Intraluminal</th>
<th>SHR Intraluminal</th>
<th>WKY Extraluminal</th>
<th>SHR Extraluminal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE, +END</td>
<td>5.25±0.09</td>
<td>5.55±0.09*</td>
<td>5.51±0.06</td>
<td>5.72±0.05*</td>
</tr>
<tr>
<td>NE, -END</td>
<td>5.69±0.04</td>
<td>5.66±0.04</td>
<td>5.80±0.10</td>
<td>5.73±0.06</td>
</tr>
<tr>
<td>ACH</td>
<td>6.57±0.29</td>
<td>5.58±0.43*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SNP</td>
<td>5.97±0.22</td>
<td>6.07±0.20</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*P<.05, tP<.01, WKY vs SHR.

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could result from either a functional change in endothelial or smooth muscle cells or morphological modifications in the vascular wall resulting in an increase of the diffusion pathway for endothelial cell vasodilators to reach the smooth muscle. However, in the present study impairment of endothelium-dependent relaxation occurred at both the high and low concentrations of acetylcholine. If limited diffusion were the cause of impaired relaxation, then only the low acetylcholine concentrations would be associated with reduced relaxation. Indeed, even after morphological modifications in the vascular wall have been established in hypertension, which take several weeks to reverse, endothelium-dependent relaxation can be quickly restored by reversing the hypertension before regression of the arterial structural thickening occurs. Therefore, it is most likely that impaired relaxation is due to a functional modification in the resistance artery, resulting in decreased endothelium-dependent relaxation possibly due to decreased synthesis or release of EDRF. Because relax-
FIG 7. Line graph shows acetylcholine (Ach) concentration-response relations for spontaneously hypertensive rat (SHR) and Wistar-Kyoto (WKY) rat mesenteric resistance arteries preconstricted with norepinephrine. Both drugs were applied intraluminally. P < .001 with repeated-measures analysis of variance. *P < .01, 10^-6 vs 10^-5 M acetylcholine for SHR; n = 7 and 8 for WKY and SHR, respectively. Error bars indicate ±SEM.

In summary, in the presence of flow, mesenteric resistance arteries are characterized by endothelial dysfunction that contributes to an increased sensitivity to the vasconstrictor norepinephrine and decreased acetylcholine-mediated vasodilatation, thereby providing a potential pathogenic role for endothelial dysfunction contributing to the increased peripheral resistance in hypertensive vascular disease.

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