Influence of Altitude Exposure on Coronary Flow Reserve

Christophe A. Wyss, MD*; Pascal Koeppfli, MD*; Gregory Fretz, MD; Magdalena Seebauer, PhD; Christian Schirlo, MD; Philipp A. Kaufmann, MD

Background — Although no data exist on the effect of altitude exposure on coronary flow reserve (CFR), patients with coronary artery disease (CAD) are advised not to exceed moderate altitudes of ≈2500 m above sea level. We studied the influence of altitude exposure on myocardial blood flow (MBF) in controls and CAD patients.

Methods and Results — In 10 healthy controls and 8 patients with CAD, MBF was measured by positron emission tomography and 15O-labeled water at rest, during adenosine stress, and after supine bicycle exercise. This protocol was repeated during inhalation of a hypoxic gas mixture corresponding to an altitude of 4500 m (controls) and 2500 m (CAD). Workload was targeted to comparable heart rate–blood pressure products at normoxia and hypoxia. Resting MBF increased significantly in controls at 4500 m (+24%, P<0.01) and in CAD patients at 2500 m (+24%, P<0.05). Altitude had no influence on adenosine-induced hyperemia and CFR. Exercise-induced hyperemia increased significantly in controls (+38%, P<0.01) at 4500 m (despite a reduction in workload, −28%, P<0.0001) but not in CAD patients at 2500 m (moderate decrease in workload, −11%, P<0.05). Exercise-induced reserve was preserved in controls (+10%, P=NS) but decreased in CAD patients (−18%, P<0.005).

Conclusions — At 2500 m altitude, there is a significant decrease in exercise-induced reserve in CAD patients, indicating that compensatory mechanisms might be exhausted even at moderate altitudes, whereas healthy controls have preserved reserve up to 4500 m. Thus, patients with CAD and impaired CFR should be cautious when performing physical exercise even at moderate altitude. (Circulation. 2003;108:1202-1207.)

Key Words: blood flow ■ hypoxia ■ exercise ■ coronary disease ■ tomography

Respiratory, circulatory, and ECG changes have been extensively described in previous studies during standardized exposure to high altitude.1 In patients with marginal cardiocirculatory function, these effects are potentially dangerous and might lead to cardiac decompensation. In patients with coronary artery disease (CAD) and a history of myocardial infarction, an increase in episodes of silent ischemia was found at an altitude of 2000 m not only during physical activities but also during normal daily activities.2 For safety reasons, it is therefore current clinical practice to advise patients with CAD not to exceed moderate altitudes of ≈2000 to 2500 m.3 Because similar conditions are encountered in most airplanes during flight, concerns have been raised about the risk of air travel for certain patients with CAD.4

In experimental animals, acute5 and chronic hypoxemia have been shown to increase baseline6 as well as maximal7 pharmacologically and exercise-induced8 myocardial blood flow (MBF). By contrast, in humans, only scant data exist on the influence of acute hypoxia on coronary circulation. A close relation between cardiac effort, myocardial O2 consumption, and coronary flow has been repeatedly reported.7,8 Because most of the O2 is normally removed from the coronary blood, an increase in O2 delivery must be achieved primarily by increased MBF. We have recently reported that high-altitude exposure increases resting MBF in healthy controls.9 It remains unclear, however, how this affects coronary flow reserve (CFR). Thus, the aim of the present study was to assess the influence of altitude exposure on adenosine- and physical exercise–induced, hyperemic MBF and CFR in nonacclimated healthy controls and in CAD patients.

Methods

Study Population

The control group consisted of 10 healthy, nonacclimated, male volunteers (mean age, 23±2 years; range, 21 to 27 years). None of the subjects had a history of cardiovascular disease or smoking. Further inclusion criteria were normal heart rate, blood pressure, and ECG and a low probability for CAD.10

The patient group included 8 nonacclimated, male patients (mean age, 36±9 years; range, 42 to 69 years) with angiographically documented CAD, ie, a luminal area stenosis of >50% in 1 (3 patients), 2 (4 patients), or 3 (1 patient) coronary vessels. All patients had stable CAD in the Canadian Cardiovascular Society (CCS) functional class II to III. Only patients with mild (>50% to 70%) or

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moderate (>70% to 90%) lesions were included. All study participants reside at an altitude of ~450 m and had not been exposed to higher altitudes for at least 6 weeks before the study.

Study Protocol
With the subject’s feet attached to a bicycle ergometer (model 380 B; Siemens-Elema AG), MBF was measured at rest and was repeated during adenosine-induced hyperemia after a 10-minute period to allow for decay of the $^{15}$O radioactivity in the body. Adenosine was infused for 7 minutes at 140 $\mu$g · kg body weight$^{-1}$·min$^{-1}$ according to standard practice. Three minutes after beginning the adenosine infusion, hyperemic MBF measurement was started. After a 10-minute interval, exercise started at 50 to 75 W with workload increments of 25 to 50 W to reach 70% of the predicted value for upright bicycle exercise within a comparable time period in all subjects. MBF was measured immediately after the end of exercise, as previously documented. Patient positioning for each image set was aided by marking the patient’s chest with a felt-tip pen and aligning the marks with the reference laser beam of the tomograph. A 20-minute transmission scan was then acquired for the purpose of attenuation correction of all emission scans and which allowed for recovery of the subjects after physical exercise. All measurements were subsequently repeated during hypoxia that simulated the respective altitude. This study protocol was approved by the institutional review board of the University Hospital Zurich, and radiation exposure was licensed by the Swiss Federal Office of Public Health, Division of Radioprotection. All subjects gave informed, written consent before the study.

Altitude Simulation
Altitude (hypoxia) was simulated by inhalation of a hypoxic gas mixture (through a mouthpiece), consisting of ~16.5% $O_2$ and 12.5% $N_2$, resulting in $O_2$ pressures of 119 mm Hg and 90 mm Hg, which corresponded to altitudes of 2500 m and 4500 m, respectively. Heart rate and peripheral arterial $O_2$ saturation (SaO$_2$) were recorded with a finger pulse oximeter (Nellcor N-200E, Nellcor Inc). Blood pressure was continuously monitored with a monitor (Finapres BP monitor, BOC Inc) and recorded at 1-minute intervals. The ECG was monitored continuously, and a 12-lead ECG was recorded at baseline and every minute during adenosine administration, as well as at each exercise level and during the 10 minutes of recovery. Additionally, the end-tidal partial pressure of $CO_2$ (Pet$CO_2$) and respiratory frequency were determined with a capnograph (Capnomatic, Dräger). After a cardiorespiratory steady state was achieved, as assessed by a steady Pet$CO_2$, SaO$_2$, and heart rate, positron emission tomography (PET) measurements were performed. For safety reasons, CAD patients were only exposed to a simulated altitude of 2500 m, whereas volunteers were exposed to a simulated altitude of 4500 m. Cardiorespiratory reactions during normobaric hypoxia and altitude have been shown to be identical for at least the first hours of exposure.

Image Acquisition
Scanning was performed at the PET Center of the University Hospital, Zurich, on a PET system (GE Advance, GE Medical Systems), which records 35 image planes simultaneously. The axial field of view was 14.5 cm. A 30-minute blank scan was recorded as part of the daily routine procedures. The optimal imaging position was determined by a 2-minute rectilinear scan after exposure of an external $^{68}$Ge ring source. An intravenous bolus of $[15O]$water (500 to 700 MBq) was infused over 20 seconds at rate of 10 mL/min to assess MBF. The line was then flushed for another 2 minutes. The dynamic image sequences were 14×5, 3×10, 3×20, and 4×30 seconds.

Image Processing
The sinograms were corrected for attenuation and reconstructed on a computer workstation (Sun workstation, Sun Microsystems). Images were transferred to another computer (Transtec 2200PC computer, Transtec AG) and analyzed with the PMOD software package (www.pmod.ch), as previously validated. Myocardial images were then generated directly from the dynamic $^{15}$O-water study to draw regions of interest, thus avoiding the need for additional $^{15}$O/CO blood pool scans. In brief, the factor sinograms were generated by means of linear dimension reduction of the dynamic sinograms, where the required variate and covariate factors (the myocardial and blood time-activity curves) were modeled from the lung time-activity curve as previously reported. The regions were drawn semiautomatically by using a centerline within the myocardium. The junctions of right and left ventricles were marked to indicate the septum. The left ventricular free wall was then subdivided geometrically into 3 segments of the same size. Arterial and tissue activity curves were fitted to a single tissue compartment tracer-kinetic model to give values of regional and global MBF (in mL · min$^{-1}$ · g$^{-1}$), as previously described. For the present analysis, the segments were grouped to obtain a value for those segments supplied by stenosed vessels and a value for a remote segment (in CAD patients), as well as a mean global value for the entire left ventricle (in controls and CAD patients).

CFR and Exercise-Induced Reserve
CFR was defined as the ratio of MBF during pharmacological hyperemia to MBF at rest and was calculated at baseline and during hypoxia. Similarly, exercise-induced reserve was defined as the ratio of MBF after bicycle exercise stress to MBF at rest. MBF utilization after exercise was expressed as a percentage of maximal hyperemic flow during pharmacological stress to indicate how much of the maximal (adenosine-induced) hyperemia could be achieved by bicycle stress. $O_2$ delivery to myocardial tissue was calculated for the remote and stenotic segments in CAD patients as hemoglobin (g/L)×SaO$_2$ (%)×MBF (mL · min$^{-1}$ · g$^{-1}$)×1.34 (mL O$_2$/g hemoglobin).

Statistical Analysis
Mean values are given with their SD. Comparisons of hemodynamic and MBF values between the different study conditions were performed by ANOVA statistics for repeated measures. When the value for $P$ was <0.05, Sheffe’s procedure was applied. For paired comparison of stenotic versus remote segments within the CAD patients, a paired $t$ test was used.

Results
Hemodynamic, ECG, and Clinical Findings
In both groups, heart rate and rate-pressure product (RPP) at rest increased significantly during hypoxia. The adenosine-induced increase in RPP during hypoxia was more pronounced in CAD patients. In controls, RPP at maximal exercise was similar at normoxia (21 193 ± 2012 mm Hg×bpm) and at hypoxia (21 138 ± 2690 mm Hg×bpm, $P=NS$) according to the study protocol, whereas workload decreased significantly, from 134 ± 19 to 96 ± 16 W (−28%, $P<0.0001$). Similarly, RPP in CAD patients was not affected by hypoxia (18 141 ± 2250 mm Hg×bpm versus 17 867 ± 3013 mm Hg×bpm, $P=NS$), whereas workload decreased from 93 ± 16 to 83 ± 19 W (−11%, $P<0.05$) at hypoxia (Table 1). At baseline level, 4 of the 8 CAD patients had significant ST-segment depression, whereas all 8 patients had ST-segment depression at simulated altitude. Similarly, 2 of the patients experienced anginal pain at baseline, but 7 did so at altitude. Maximal ST-segment depression averaged 1.5 mm at baseline versus 2.0 mm at hypoxia ($P=NS$).

Respiratory Parameters
There was significant hypoxic hyperventilation in controls at 4500 m, with a decrease in Pet$CO_2$ from 37 ± 3 to 33 ± 5 mm Hg ($P<0.005$) but not in patients at 2500 m (35 ± 5...
TABLE 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia*</th>
<th>P</th>
<th>Normoxia</th>
<th>Hypoxia*</th>
<th>P</th>
<th>Normoxia</th>
<th>Hypoxia*</th>
<th>P</th>
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<tbody>
<tr>
<td>Controls (n=10)</td>
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<tr>
<td>SBP, mm Hg</td>
<td>117±17</td>
<td>126±27</td>
<td>NS</td>
<td>121±14</td>
<td>130±18</td>
<td>NS</td>
<td>165±11</td>
<td>160±20</td>
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<td>70±15</td>
<td>NS</td>
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<td>NS</td>
<td>87±17</td>
<td>81±17</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>81±14</td>
<td>87±14</td>
<td>NS</td>
<td>85±19</td>
<td>90±15</td>
<td>NS</td>
<td>113±14</td>
<td>107±17</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>63±7</td>
<td>79±8</td>
<td>&lt;0.0001</td>
<td>91±10</td>
<td>100±12</td>
<td>NS</td>
<td>129±8</td>
<td>133±8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RPP, bpm×mm Hg</td>
<td>7380±1252</td>
<td>9589±1390</td>
<td>&lt;0.0005</td>
<td>11 469±2605</td>
<td>13 049±2686</td>
<td>NS</td>
<td>21 193±2012</td>
<td>21 138±2690</td>
<td>NS</td>
</tr>
<tr>
<td>CAD patients (n=8)</td>
<td></td>
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<tr>
<td>SBP, mm Hg</td>
<td>119±24</td>
<td>128±13</td>
<td>NS</td>
<td>120±15</td>
<td>130±18</td>
<td>NS</td>
<td>161±22</td>
<td>159±19</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>58±13</td>
<td>73±7</td>
<td>&lt;0.005</td>
<td>60±14</td>
<td>74±13</td>
<td>&lt;0.05</td>
<td>84±14</td>
<td>93±18</td>
<td>NS</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>78±16</td>
<td>92±8</td>
<td>&lt;0.05</td>
<td>80±14</td>
<td>93±14</td>
<td>&lt;0.05</td>
<td>109±15</td>
<td>115±17</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>62±7</td>
<td>72±11</td>
<td>&lt;0.0005</td>
<td>83±9</td>
<td>89±12</td>
<td>&lt;0.05</td>
<td>114±10</td>
<td>112±10</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, bpm×mm Hg</td>
<td>7301±1310</td>
<td>9276±1772</td>
<td>&lt;0.05</td>
<td>9918±1097</td>
<td>11 486±1785</td>
<td>&lt;0.05</td>
<td>18 141±2250</td>
<td>17 867±3013</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; and HR, heart rate.

*Hypoxia at a simulated altitude of 4500 m above sea level for controls and 2500 m above sea level for CAD patients.

Mean resting MBF increased significantly (+24%, P<0.01) from baseline (Zurich, 450 m) to 4500 m. Bicycle exercise–induced, hyperemic MBF increased by 38% (P<0.01, Figure 1), whereas adenosine-induced hyperemic MBF showed no significant change at altitude (+11%, P=NS). Adenosine-induced CFR was comparable at normoxia and hypoxia (4.02±1.00 versus 3.48±0.95 mL·min⁻¹·g⁻¹, P=NS). Similarly, exercise-induced reserve was not affected by hypoxia (1.72±0.31 versus 1.77±0.34 mL·min⁻¹·g⁻¹, P=NS, Figure 2).

Mean resting MBF increased significantly (+24%, P<0.05) from baseline to 2500 m. Adenosine-induced, hyperemic MBF showed a nonsignificant trend (+17%) toward an increase, whereas bicycle exercise–induced, hyperemic MBF was not affected by hypoxia (+0%). As a result, there was no change in adenosine-induced CFR from normoxia to hypoxia (2.26±0.35 versus 2.15±0.58 mL·min⁻¹·g⁻¹, P=NS). By contrast, bicycle exercise–induced reserve decreased significantly, by −18%, from normoxia to hypoxia (2.13±0.48 versus 1.79±0.63 mL·min⁻¹·g⁻¹, P<0.005, Table 2 and Figure 2). In controls, MBF utilization was 47±18% at baseline and 49±11% during hypoxia, but MBF was significantly higher in CAD patients, with values of 96±29% and 84±21%, respectively (P<0.0001 versus controls), indicating exhaustion of the available MBF utilization in CAD patients.

**Segmental Data in CAD Patients**

In remote segments, hypoxia induced a significant MBF increase at rest (1.07 versus 1.35 mL·min⁻¹·g⁻¹, P<0.05) but not during adenosine (2.68 versus 3.46 mL·min⁻¹·g⁻¹, P=NS) or after bicycle exercise (2.34 versus 2.61 mL·min⁻¹·g⁻¹, P=NS). Thus, adenosine-induced CFR showed no change (2.50 versus 2.53, P=NS), and exercise-induced reserve tended to decrease slightly (2.24 versus 2.15 mL·min⁻¹·g⁻¹, P=NS).

In stenotic segments, hypoxia induced a significant MBF increase at rest (1.01 versus 1.29 mL·min⁻¹·g⁻¹, P<0.05) but not during adenosine (2.26 versus 2.49 mL·min⁻¹·g⁻¹, P=NS). Exercise-induced reserve in controls but significant decrease in CAD patients.

**Figure 1.** Hypoxia-induced mismatch was found at exercise between MBF and workload.

**Figure 2.** Hypoxia induced trend toward increase in exercise-induced reserve in controls but significant decrease in CAD patients.
Table 2. MBF, CFR, and Exercise-Induced Reserve

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Adenosine</th>
<th>Exercise</th>
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<tr>
<td></td>
<td>Normoxia</td>
<td>Hypoxia*</td>
<td>Δ%</td>
</tr>
<tr>
<td>Controls (n=10)</td>
<td>1.14 ± 0.22</td>
<td>1.40 ± 0.29</td>
<td>+24</td>
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<tr>
<td>MBF, mL · min⁻¹ · g⁻¹</td>
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<tr>
<td>CFR†</td>
<td>...</td>
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<tr>
<td>Global</td>
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<td>Remote</td>
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<tr>
<td>Stenotic</td>
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<tr>
<td>Mild (&gt;50% to 70%)</td>
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<td>Moderate (&gt;70% to 90%)</td>
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| ≈Hypoxia at a simulated altitude of 4500 m above sea level for controls and 2500 m above sea level for CAD patients.†CFR given as relative value.

P=NS). After exercise, there was a nonsignificant decrease in MBF (2.29 versus 2.00 mL · min⁻¹ · g⁻¹, P=NS). Adenosine-induced CFR was unchanged (2.12 versus 1.95, P=NS), whereas exercise-induced reserve decreased significantly by 23% (2.07 versus 1.58, P<0.01). Values for CFR tended to be lower in segments supplied by coronary arteries with more severe lesions (Table 2).

During bicycle exercise, O₂ delivery to remote segments of CAD patients was not affected by hypoxia (4.2 ± 1.4 mL O₂ · min⁻¹ · g⁻¹ myocardial tissue at normoxia versus 4.4 ± 2.4 mL O₂ · min⁻¹ · g⁻¹, P=NS), whereas it decreased significantly in stenotic segments, from 4.2 ± 1.6 to 3.3 ± 0.8 mL O₂ · min⁻¹ · g⁻¹ (P<0.05 versus normoxia and versus remote, Figure 3).

Discussion

Our data show that in healthy humans, resting and—even more pronounced—exercise-induced MBF increases at high altitudes, indicating a maintained exercise-induced reserve up to an altitude of 4500 m. By contrast, in patients with CAD, compensatory mechanisms appear to be exhausted even at moderate altitudes, because their bicycle exercise—induced reserve was decreased even at 2500 m, whereas adenosine-induced CFR remained unchanged in both groups.

Resting MBF in healthy volunteers increased significantly at high altitude, confirming our previous results. MBF is mainly determined by cardiac workload (ie, RPP) at rest and during physical exercise, but not to remote segments, indicating that compensatory response is less pronounced in remote segments than in stenotic segments.

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Figure 3. Myocardial O₂ delivery (mean±SEM) in CAD patients at exercise is significantly reduced in stenotic segments versus remote and versus normoxia (baseline, P<0.05).
mechanisms appear to be exhausted in CAD patients, even with moderate lesion severity and at a moderate altitude of 2500 m, which corresponds to the cabin pressure in most airlines during flight. Although passengers do not generally exert much physical exercise throughout most of the flight, our findings might still raise some concerns about the safety of CAD patients during air travel. In many passengers with cardiopulmonary disease, the PaO₂ at sea level is <95 mm Hg and is on the steep portion of the oxyhemoglobin-dissociation curve; at ordinary cabin pressures, the O₂ saturation might fall dramatically. For them, routine cabin pressures increase the risk of hypobaric hypoxia. The clinical importance of our results also lies in the fact that a substantial portion of the middle- and older-age population remains physically active, participating in sports at altitudes, such as skiing.

We have used bicycle exercise stress for stimulation of hyperemic MBF as a physiological stimulus reflecting the natural response of the coronary arteries, whereas a pharmacological stimulus alone might have been of limited value in the assessment of pathophysiological changes. Furthermore, the importance of a physiological exercise stress test as a powerful predictor of outcome and mortality has been recently confirmed in a large, long-term trial. However, only very few reports in the literature deal with the use of physical exercise in PET, and only recently has its reproducibility been documented. In the present study, exercise-induced, hyperemic flow was higher in patients than in controls, possibly indicating an uncoupling of MBF and cardiac work due to inefficient contractility of the ischemic heart. In fact, as patients had a significantly decreased maximal adenosine-induced MBF, they utilized ~90% of their available maximal MBF during physical exercise. By contrast, controls utilized <50% of their maximal MBF.

A first limitation of the present study is that subjects did not exercise at their maximal level of effort owing to the fact that exercise workload in the supine position usually matches ~70% of the workload achieved in the upright position. In addition, physical capacity at high altitudes of 5000 m has been found to match 70% of the capacity at sea level.

Second, data were acquired in the immediate postexercise period, when the cardiac power output is considerably decreased and when flow is also expected to fall rapidly. These suboptimal conditions were chosen as a compromise to permit the subjects' recovery after exercise within a reasonable time and to avoid excessive motion artifact during scanning, but it might have diminished hypoxia-induced changes. However, the fact that every subject served as his own control strengthens our results.

Third, the age in CAD patients was higher than in controls, and no women were included. However, no sex difference and no difference in the physiological response to hypoxia over a wide age range from 8 to 83 years have been reported. We have previously found, for a large number of subjects, that resting MBF was slightly higher in women than in men but that no sex differences existed during hyperemia. Although we have no data on female volunteers in the present study, one can reasonably anticipate that potential sex differences would not have significantly changed our results with regard to stress perfusion measurement.

Finally, exercise induced an increase in respiratory rate, which could have affected MBF measurements. Because maximal respiratory rate was not affected by hypoxia in either group and each individual served as his own control, changes in respiratory rate might not have significantly affected measurements, although no respiratory gating was performed. This is in line with the fact that no respiratory gating is performed for routine adenosine stress, although tachypnea occurs in one third of patients.

In conclusion, our results show that exercise-induced flow reserve is maintained in healthy volunteers during high-altitude exposure, whereas it is significantly decreased in CAD patients, even at moderate altitude. These findings might support the concept that patients with reduced CFR, as observed in CAD, should be warned to refrain from physical exercise, even at exposure to moderate altitudes.

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