

**ORIGINAL ARTICLE**

Association between Pulse Pressure and Impaired Pulmonary Function in Non-Smoking Adults

Hyun Yoon

Department of Clinical Laboratory Science, Wonkwang Health Science University, Iksan, Korea

비흡연 성인에서 맥압과 폐기능 장애의 상관성

윤 현

원광보건대학교 임상병리과

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ABSTRACT

According to previous studies, an impaired pulmonary function is associated with arterial stiffness (AS). The pulse pressure (PP) is an important predictor of AS, but the association of an impaired pulmonary function with the PP is unclear. Therefore, this study assessed the associations between the PP and the predicted forced vital capacity (predicted FVC) and predicted forced expiratory volume in one second (predicted FEV₁) in Korean non-smoking adults. The data obtained from 6,857 adults during the 2013~2015 Korean National Health and Nutrition Examination Survey were analyzed. After adjusting for the related variables, the ORs of restrictive pulmonary disease (RPD, the predicted FVC<80.0% with FEV₁/FVC≥70.0%) using the normal PP group (PP≤60 mmHg) as a reference group was significant for the high PP group (PP>60 mmHg; 1.337 [95% confidence interval (CI), 1.049~1.703]). In addition, the ORs of obstructive pulmonary disease (OPD, FEV₁/FVC<70.0%) using the normal PP group as a reference group were significant for the high PP group (1.339 [95% CI, 1.093~1.642]). In conclusion, a high PP is positively associated with both RPD and OPD in Korean non-smoking adults.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the leading cause of mortality in high- (5.0%) and middle-income countries (6.9%) [1]. Impaired lung function, which is indicated by reduced forced expiratory volume in forced vital capacity (FVC) and first second of exhalation (FEV₁), contributes significantly to cardio- and cerebrovascular events and mortality [2, 3].

Impaired lung function occurs due to smoking, hypertension, chronic kidney disease, and type 2 diabetes mellitus [4, 5]. Some previous studies reported that arterial stiffness (AS) is increased in COPD [6-8]. It has been suggested that a link between vascular and pulmonary disease may explain a proportion of the excess cardiovascular mortality in COPD.

Pulse pressure (PP), which is the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP), is known to be a strong risk factor for cardiovascular events and mortality or all-cause mortality [9, 10]. In addition, PP is an important predictor of AS and pulse wave velocity (PWV) because PP is determined by the elastic of the large arteries and the

Corresponding author: Hyun Yoon
 Department of Clinical Laboratory Science, Wonkwang Health Science University,
 514 Iksan-daero, Iksan 54538, Korea
 E-mail: yh9074@yahoo.co.kr
 ORCID: <https://orcid.org/0000-0002-4741-9664>



magnitude of wave reflections [11, 12]. However, little research exists regarding the relationship between PP and impaired pulmonary function. Therefore, this study aimed to investigate the association between PP and impaired pulmonary function in Korean non-smoking adults aged ≥ 20 years using the data obtained in 2013~2015 from the sixth Korean National Health and Nutrition Examination Survey (KNHANES-VI).

MATERIALS AND METHODS

1. Subjects

This study was based on most recent data from the KNHANES VI (2013~2015). The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. KNHANES comprises a health interview survey, a health behavior survey, a health examination survey, and a nutrition survey. Households as sampling units were stratified and collected through a multistage, probability-based sampling design based on sex, age, and geographic area, using household registries. At the time each survey was done, participants provided written informed consent for use of their data in further analyses and were given the right to refuse to participate, in accordance with the National Health Enhancement Act. In the KNHANES VI, 22,948 individuals over age 1 were sampled for the survey. We excluded 13,524 subjects who were missing for pulmonary function test, and those (592 subjects) for whom data were missing for important analytic variables, such as various blood chemistry tests. In addition, we excluded the current-smoker (1,975 subjects who smoked more than one cigarette a day). Finally, 6,857 subjects were included in the statistical analysis. The KNHANES VI study has been conducted according to the principles expressed in the Declaration of Helsinki (2013-07CON-03-4C, 2013-12EXP-03-5C, 2015-01-02-6C). All survey participants agreed with the use of epidemiological research to identify risk factors and death causes of chronic

diseases. Participants' records and information in the KNHANES were anonymous and de-identified prior to analysis. Further information can be found in "The KNHANES V Sample," which is available on the KNHANES website. The official website of KNHANES (<http://knhanes.cdc.go.kr>) is currently operating an English-language information homepage. The data of the respective year are available to everyone free of charge. If the applicant completes a simple subscription process and provides his/her email address on the official website of KNHANES, the data of the respective year can be downloaded free of charge. If additional information is required, the readers may contact the department responsible for the storage of data directly (Su Yeon Park, sun4070@korea.kr).

2. General characteristics and blood chemistry

Research subjects were classified by gender and by age into less than 50 years, 50~59 years, 60~69 years, and 70 years or older. Research subjects were classified by sex (men and women), alcohol drinking (yes or no), and regular exercise (yes or no). Alcohol drinking was indicated as "yes" for participants who had consumed at least one glass of alcohol every month over the last year. Regular exercise was indicated as "yes" for participants who had exercised on a regular basis regardless of indoor or outdoor exercise. Regular exercise was defined as 30 min at a time and 5 times/wk in the case of moderate exercise, such as swimming slowly, doubles tennis, volleyball, badminton, table tennis, and carrying light objects; and for 20 min at a time and 3 times/wk in the case of vigorous exercise, such as running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, singles tennis, and carrying heavy objects. Anthropometric measurements included body mass index (BMI), waist measurement (WM), SBP, and DBP. Blood chemistry included measurement of triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), predicted forced vital capacity (predicted FVC), predicted forced expiratory volume in 1

second (predicted FEV₁), and FEV₁/FVC.

3. Definitions of PP, RPD, OPD

PP was calculated as the difference between SBP and DBP. High PP was classified when the PP was >60 mmHg [13] because the cutoff for the high PP was not yet clear. The obstructive pulmonary disease (OPD) was defined FEV₁/FVC<70.0% and restrictive pulmonary disease (RPD) was defined the predicted FVC<80.0% with FEV₁/FVC≥70.0% [14, 15].

4. Statistical analysis

The collected data were statistically analyzed using SPSS WIN version 18.0 (SPSS Inc., Chicago, IL, USA). The distributions of the participant characteristics were converted into percentages, and the successive data were presented as averages with standard deviations. The distribution and average difference in clinical characteristics and iron related indices according to normal PP and high PP were calculated

using chi-squared and an independent t test. Multiple linear regression analysis models were constructed for the predicted FVC and FEV₁ and FEV₁/FVC: model 2) were adjusted for age, gender, drinking alcohol, regular exercise, TGs, HDL-C, FBG, BMI, WM, and either SBP and DBP or PP. In the case of logistic regression for odds ratio of OPD and RPD, the 4 models constructed were: 1) non-adjusted; 2) adjusted for age, gender, drinking, and regular exercising; 3) further adjusted for TGs, HDL-C, and FBG; 4) further adjusted for BMI and WM. The significance level for all of the statistical data was set as *P*<0.05.

RESULTS

1. Clinical characteristics of research subjects

The clinical characteristics of the research subjects are shown in Table 1. The prevalence rates of high PP in men and women were 346 (14.3%) and 617 (13.6%), respectively. The prevalence rates of RPD and OPD

Table 1. General characteristics of research subjects

N (%), Mean±SD, (N=6,857)

Variables	Category	Total (N=6,857)	Men (N=2,427)	Women (N=4,430)	<i>P</i>
Age (years)		57.63±10.58	59.08±10.84	56.83±10.35	<0.001
	<50	1,799 (26.3)	556 (22.9)	1,243 (28.1)	<0.001
	50~59	2,119 (30.9)	680 (28.1)	1,439 (32.5)	
	60~69	1,793 (26.1)	702 (28.9)	1,091 (24.6)	
	≥70	1,146 (16.7)	489 (20.1)	657 (14.8)	
Alcohol drinking	Yes	3,049 (44.5)	1,553 (64.0)	1,496 (33.8)	<0.001
Regular exercising	Yes	1,619 (23.6)	882 (36.3)	737 (16.6)	<0.001
SBP (mmHg)		120.79±16.78	122.91±15.76	119.63±17.21	<0.001
DBP (mmHg)		75.87±10.02	78.00±10.25	74.70±9.69	<0.001
PP (mmHg)		44.92±13.41	44.91±13.31	44.93±13.47	0.946
High PP		963 (14.0)	346 (14.3)	617 (13.6)	0.708
BMI (kg/m ²)		24.15±3.07	24.46±2.89	23.98±3.14	<0.001
WM (cm)		82.27±9.03	86.11±8.23	80.17±8.75	<0.001
TGs (mg/dL)		134.86±94.34	154.57±117.12	124.07±77.03	<0.001
HDL-C (mg/dL)		80.78±11.99	47.25±11.19	52.71±11.98	<0.001
FBG (mg/dL)		102.04±22.46	106.33±24.82	99.70±20.69	<0.001
Predicted FVC (%)		93.31±11.83	91.31±11.94	94.41±11.62	<0.001
Predicted FEV ₁ (%)		93.29±13.41	91.01±14.20	94.54±12.80	<0.001
FEV ₁ /FVC (%)		77.69±7.26	74.70±8.38	79.33±5.96	<0.001
RPD		569 (8.3)	229 (9.4)	340 (7.7)	<0.001
OPD		828 (12.1)	543 (22.4)	285 (6.4)	<0.001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; High PP, PP>60 mmHg; WM, waist measurement; BMI, body mass index; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; Predicted FVC, predicted forced vital capacity; Predicted FEV₁, predicted forced expiratory volume in 1 second; RPD, restrictive pulmonary diseases, predicted FVC<80.0% with FEV₁/FVC≥70.0%; OPD, obstructive pulmonary diseases, FEV₁/FVC<70.0%.

were 569 (8.3%) and 828 (12.1%), respectively. The following parameters were significantly higher ($P < 0.001$) in men than in women: alcohol intake, regular exercise, SBP, DBP, BMI, WM, TGs, FBG, OPD, and RPD. However, the following were significantly lower ($P < 0.001$) in men than in women: HDL, predicted FVC, predicted FEV₁, and FEV₁/FVC.

2. Clinical characteristics of subjects according to normal and high pulse pressure

The clinical characteristics of subjects according to

normal and high PP are shown in Table 2. Age ($P < 0.001$), BMI ($P < 0.001$), WM ($P < 0.001$), SBP ($P < 0.001$), DBP ($P = 0.005$), PP ($P < 0.001$), TGs ($P < 0.001$), and FBG ($P < 0.001$) were higher in the high PP group than in the normal PP group. HDL-C ($P < 0.001$), predicted FVC ($P < 0.001$), and FEV₁/FVC ($P < 0.001$) were lower in the high PP group than in the normal PP group, but predicted FEV₁ ($P = 0.223$) was not significant.

Table 2. Clinical characteristics of subjects according to normal and high pulse pressure

N (%), Mean \pm SD, (N=6,857)

Variables	Normal PP (N=5,894)	High PP (N=963)	<i>P</i>
Age (years)	56.00 \pm 10.04	67.63 \pm 7.95	<0.001
Women	3,813 (64.7)	617 (64.1)	0.708
Alcohol drinker	2,718 (46.1)	331 (34.4)	<0.001
Regular exerciser	1,407 (23.9)	212 (22.0)	0.208
BMI (kg/m ²)	24.10 \pm 3.09	24.51 \pm 2.95	<0.001
WM (cm)	81.88 \pm 9.07	84.66 \pm 8.37	<0.001
SBP (mmHg)	116.86 \pm 13.70	144.83 \pm 13.58	<0.001
DBP (mmHg)	76.00 \pm 9.73	75.02 \pm 11.57	0.005
PP (mmHg)	40.86 \pm 8.73	69.81 \pm 9.67	<0.001
TGs (mg/dL)	133.11 \pm 92.96	145.62 \pm 101.73	<0.001
HDL-C (mg/dL)	50.98 \pm 12.01	49.50 \pm 11.83	<0.001
FBG (mg/dL)	101.12 \pm 21.87	107.71 \pm 25.06	<0.001
Predicted FVC (%)	93.81 \pm 11.58	90.28 \pm 12.82	<0.001
Predicted FEV ₁ (%)	93.37 \pm 12.96	92.80 \pm 15.92	0.223
FEV ₁ /FVC (%)	78.09 \pm 7.03	75.24 \pm 8.13	<0.001
Restrictive pulmonary diseases	456 (7.7)	113 (11.7)	<0.001
Obstructive pulmonary diseases	629 (10.7)	199 (20.7)	<0.001

Abbreviations: See Table 1; Normal PP, PP \leq 60 mmHg; High PP, PP $>$ 60 mmHg.

Table 3. Multiple linear regression analysis for the independent factors determining predicted FVC

(N=6,857)

Variables	Predicted FVC (%)					
	β	95% CI	<i>P</i>	β	95% CI	<i>P</i>
Age (years)	-0.068	-0.108 to -0.043	<0.001	-0.066	-0.106 to -0.042	<0.001
Women	0.058	0.750 to 2.121	<0.001	0.059	0.787 to 2.146	<0.001
Current drinker	-0.005	-0.710 to 0.452	0.663	-0.006	-0.714 to 0.447	0.652
Regular exerciser	-0.012	-0.994 to 0.306	0.299	-0.012	-0.998 to 0.302	0.294
BMI (kg/m ²)	-0.087	-0.501 to -0.170	<0.001	-0.089	-0.507 to -0.178	<0.001
WM (cm)	-0.096	-0.186 to -0.065	<0.001	-0.096	-0.186 to -0.065	<0.001
TGs (mg/dL)	0.003	-0.003 to 0.004	0.810	0.002	-0.003 to 0.003	0.868
HDL-C (mg/dL)	0.047	0.020 to 0.072	<0.001	0.046	0.020 to 0.071	<0.001
FBG (mg/dL)	-0.062	-0.045 to -0.020	<0.001	-0.062	-0.045 to -0.020	<0.001
SBP (mmHg)	-0.092	-0.089 to -0.041	<0.001		None	
DBP (mmHg)	0.047	0.017 to 0.095	0.005		None	
PP (mmHg)		None		-0.075	-0.090 to -0.041	<0.001

Abbreviations: See Table 1.

3. Multiple linear regression analyses for the independent factors determining predicted FVC and FEV₁

The multiple linear regression analyses for the independent factors that determine predicted FVC and FEV₁ are shown in Tables 3 and 4. We used a multivariate model adjusted for confounders that may be significantly associated with the dependent variables (predicted FVC and FEV₁). Predicted FVC was inversely associated with SBP ($P < 0.001$) and PP ($P < 0.001$) but positively associated with DBP ($P = 0.005$). Predicted FEV₁ was inversely associated with SBP ($P = 0.031$) and PP ($P = 0.029$) but not associated with DBP ($P = 0.221$).

4. Comparisons of the odds ratio of high pulse pressure according obstructive and restrictive pulmonary diseases

The comparisons of RPD and OPD for high PP are shown in Table 5. After adjustment for related variables (age, gender, alcohol drinking, regular exercise, TGs, HDL-C, FBG, BMI, and WM), the odds ratios (ORs) of a high PP with the normal group as a reference were significantly higher in the RPD group (1.337 [95% CI, 1.049~1.703]) and OPD group (1.339 [95% CI, 1.093~1.642]).

DISCUSSION

This study investigated the association between PP and impaired pulmonary function in Korean non-smoking adults using data from the KNHANES-VI,

Table 4. Multiple linear regression analysis for the independent factors determining predicted FEV₁ (N=6,857)

Variables	Predicted FEV ₁ (%)					
	β	95% CI	P	β	95% CI	P
Age (years)	0.064	0.043 to 0.119	<0.001	0.064	0.044 to 0.119	<0.001
Women	0.067	1.083 to 2.685	<0.001	0.068	1.100 to 2.687	<0.001
Current drinker	-0.005	-0.809 to 0.549	0.707	-0.005	-0.810 to 0.547	0.704
Regular exerciser	-0.018	-1.318 to 0.201	0.150	-0.018	-1.319 to 0.200	0.149
BMI (kg/m ²)	0.112	0.295 to 0.682	<0.001	0.111	0.295 to 0.678	<0.001
WM (cm)	-0.162	-0.311 to -0.170	<0.001	-0.162	-0.311 to -0.170	<0.001
TGs (mg/dL)	-0.002	-0.004 to 0.003	0.861	-0.003	-0.004 to 0.003	0.844
HDL-C (mg/dL)	0.048	0.024 to 0.084	<0.001	0.048	0.024 to 0.083	<0.001
FBG (mg/dL)	-0.043	-0.040 to -0.011	0.001	-0.043	-0.040 to -0.011	0.001
SBP (mmHg)	-0.039	-0.060 to -0.003	0.031		None	
DBP (mmHg)	0.021	-0.017 to 0.074	0.221		None	
PP (mmHg)		None		-0.032	-0.060 to -0.003	0.029

Abbreviations: See Table 1.

Table 5. Comparisons of the odds ratio of high pulse pressure according obstructive and restrictive pulmonary diseases (N=6,857)

Variables	High PP (PP>60 mmHg)			
	Model 1	Model 2	Model 3	Model 4
Normal	1	1	1	1
Restrictive pulmonary diseases	1.872 (1.499~2.338)	1.404 (1.107~1.781)	1.365 (1.074~1.735)	1.337 (1.049~1.703)
Obstructive pulmonary diseases	2.390 (1.996~2.862)	1.333 (1.090~1.631)	1.363 (1.113~1.669)	1.339 (1.093~1.642)

Abbreviations: See Table 1; Model 1 [ORs (95% CI)], Non-adjusted; Model 2 [ORs (95% CI)], Model 1 adjusted for age, gender, alcohol drinking, and regular exercising; Model 3 [ORs (95% CI)], Model 2 further adjusted for TGs, HDL-C, and FBG; Model 4 [ORs (95% CI)], Model 3 further adjusted for BMI and WM.

which was conducted in 2013~2015. After adjusting for related variables, PP was found to be inversely associated with predicted FVC and FEV₁ and positively associated with both RPD and OPD.

Impaired lung function, as assessed by a reduction in the forced expiratory volume measured in the FEV₁ and FVC, contributes significantly to several major health issues, such as cardiovascular events and mortality, as well as all-cause mortality [16]. PP was an independent predictor of total mortality and was a more potent predictor of total mortality than SBP or DBP [17, 18]. PP is known to be a strong risk factor for arterial and peripheral vascular disease because PP is an important predictor of AS [19–21]. AS increases left ventricular pulsatile work and is associated with left ventricular hypertrophy (LVH) and alteration of cardiac function [22, 23]. PP was associated with LVH [24, 25], heart failure [26, 27], cardiac mass [28], and cardiac hypertrophy [29]. In particular, when PP and SBP increased in parallel, they have an adverse effect on cardiac hypertrophy [29].

We were investigated the association of PP and RPD and OPD in Korean non-smoking adults, using data from the KNHANES VI, and the ORs of RPD and OPD from the normal PP group as a reference group and found significant values for the high PP group (RPD, 1.337 [95% CI, 1.049~1.703]; OPD, 1.339 [95% CI, 1.093~1.642]). Currently, research on the association of PP with pulmonary disease is rare, and the mechanism behind the relationship between PP and pulmonary disease remains ambiguous. However, there are potential mechanisms that link PP with pulmonary disease. First, the association between cardiac dysfunction and abnormal pulmonary function has been previously reported [30–34]. Pelà et al [31] reported that patients with COPD exhibit significant changes in their left ventricular geometry, resulting in concentric remodeling. Olson et al [32] reported that an increase in cardiac size could place significant constraints on the pulmonary function and likely plays a major role in the restrictive patterns often reported in heart failure

patients. In addition, Kolb et al [33] suggested that right ventricular dysfunction is associated with hypoxic pulmonary vasoconstriction, pulmonary vascular remodeling, and disruption of pulmonary vascular beds due to the underlying lung disease. Second, PP can be associated with impaired pulmonary function because an increase in PP causes vascular injury to systemic and pulmonary arteries. Guntheroth suggested that increased PP produces injury in the pulmonary arteries due to the exaggerated distension of the arterial wall with each heartbeat [34]. Pulmonary artery stiffening may contribute to the progression of pulmonary hypertension by contributing to chronic microvascular damage in lungs [35]. Third, previous studies have reported that AS is associated with decreased pulmonary function. Jankowich et al reported that FEV₁ is inversely associated with AS measured by peripheral pulse pressure ($r=-0.37$, $P<0.001$) in the general population [36]. Zureik et al [37] reported that PWV was inversely associated with both FVC ($P<0.006$) and FEV₁ ($P<0.001$). They suggested that increased AS can also occur in parallel with increased pulmonary vascular resistance and vessel stiffness. In addition, patients with pulmonary arterial hypertension may show altered vascular function in systemic arteries [38].

We investigated the association between pulmonary function (predicted FVC and FEV₁) and blood pressure (SBP and DBP) and PP. Predicted FVC was inversely associated with SBP ($P<0.001$) but positively associated with DBP ($P=0.005$). Predicted FEV₁ was inversely associated with SBP ($P=0.031$) but not associated with DBP ($P=0.221$). Both predicted FVC ($P<0.001$) and FEV₁ ($P=0.029$) were inversely associated with PP. These results may be a result of the PP calculation method (the difference between SBP and DBP). An increase in PP may occur in the following cases: when SBP increases and DBP decreases; when SBP increases even if DBP does not; and when DBP decreases even if SBP does not. An increase in PP corresponds to the first and second cases in our results.

In fact, smoking is the most important factor in

impaired pulmonary function and is associated with AS and PP [39, 40]. Therefore, we excluded current smokers in our study for further clarification of the link between impaired pulmonary function and PP. The results of our study conducted on non-smokers showed that high PP was positively associated with both RPD and OPD. One of the reasons for this is that SBP increased with a decrease in predicted FVC and FEV₁, but DBP decreased with a reduction in predicted FVC (although not predicted FEV₁). Our results may also provide the fundamental data that link impaired pulmonary function with AS. The limitation of the present study was that because this study was cross-sectional, the ability to establish a causal relationship between the impaired pulmonary function and PP was limited. However, despite this limitation, this is the first study to report on the relationship between impaired pulmonary function and high PP in Korean non-smoking adults. Therefore, more accurate results may be obtained by performing a cohort study.

In conclusions, this study investigated the association of PP and impaired pulmonary function in Korean non-smoking adults using data from KNHANES-VI, which was conducted in 2013~2015. PP was inversely associated with the predicted FVC and FEV₁ levels. Increased PP was positively associated with both RPD and OPD.

요약

선행 연구에서 동맥경화와 폐기능이상과 연관성이 있었다. 맥압은 동맥경화의 중요한 예측이지만 아직까지 폐기능이상과 맥압의 연관성은 불분명하다. 따라서, 본 연구는 대한민국 비흡연 성인을 대상으로 맥압과 폐기능장애(예측 강제 폐활량, 예측 강제 날숨량 1초율)의 관련성을 알아보려고 실시하였다. 본 연구는 2013년부터 2015년까지 3년간의 대한민국 국민건강영양조사자료에서 비흡연 성인(6,857명)을 대상으로 실시하였다. 본 연구의 주요 결과는 맥압과 폐기능장애에 대한 관련 변수를 보정한 후의 결과에서, 정상 맥압(pulse pressure, PP≤60 mmHg)에 비하여 고맥압(PP>60 mmHg; 1.337 [95% confidence interval (CI), 1.049~1.703]에서 제한성 폐질환

(restrictive pulmonary disease, RPD; the predicted FVC<80.0% with FEV₁/FVC≥70.0%)의 교차비(odds ratio, OR)가 유의하게 높았다. 추가적으로, 정상맥압에 비하여 고맥압(1.339 [95% CI, 1.093~1.642])에서 폐쇄성 폐질환(obstructive pulmonary disease, OPD; FEV₁/FVC<70.0%)의 교차비가 유의하게 높았다. 결론적으로, 대한민국 비흡연 성인에서 제한성 폐질환 및 폐쇄성 폐질환은 고맥압과 유의한 관계가 있었다.

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