·临床研究·

白日嗜睡对阻塞性睡眠呼吸暂停低通气患者认知障碍的影响

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【摘 要】 目的 探讨阻塞性睡眠呼吸暂停低通气综合征(OSAHS)患者认知障碍的影响因素。**方法** 选择2018年1月至2019年12月于南京市第一医院呼吸科睡眠中心经多导睡眠监测诊断为OSAHS的患者175例,其中重度OSAHS患者96例,轻中度OSAHS患者79例。根据Epworth嗜睡量表(ESS)评分及嗜睡症状将患者分为OSAHS合并白日嗜睡(EDS)和未合并EDS,收集患者的一般资料,采用蒙特利尔认知评估量表(MoCA)评价患者的认知障碍。比较合并EDS与未合并EDS的OSAHS患者认知障碍评分,并进行相关因素分析。采用SPSS 22.0软件进行数据分析。根据数据类型,组间比较分别采用t检验及χ^2检验。采用Pearson进行相关性分析。应用多因素回归分析评价MoCA和ESS相关因素。**结果** 重度OSAHS合并EDS和不合并EDS患者氧减指数(ODI)、最低脉氧饱和度($LSaO_2$)和脉氧饱和度<90%时间占总睡眠时间百分比(TS90%)比较,差异均有统计学意义($P<0.05$);轻中度OSAHS合并EDS和未合并EDS患者ODI和TS90%比较,差异均有统计学意义(均$P<0.05$)。重度OSAHS患者较轻中度OSAHS患者视空间执行力、注意力、延迟回忆、抽象能力及定向力下降,差异均有统计学意义(均$P<0.05$)。重度OSAHS患者中合并EDS较未合并EDS患者相比MoCA总分降低,其中注意力及延迟记忆差异有统计学意义($P<0.05$);轻中度患者合并EDS较未合并EDS患者MoCA总分降低,其中仅注意力差异有统计学意义($P<0.05$)。MoCA评分和ESS、AHI、ODI、TS90呈负相关,和$LSaO_2$呈正相关,差异均有统计学意义($r=-0.432$、-0.511、-0.539、-0.420、0.458,均$P<0.01$)。ESS评分和体质量指数、腹围、腰臀比、ODI及TS90%呈正相关,和$LSaO_2$呈负相关,差异均有统计学意义($r=0.262$、0.299、0.460、0.538、0.498、-0.417,均$P<0.05$)。多因素线性回归分析显示MoCA评分和ESS评分、ODI独立相关($R^2=0.325$,$P<0.05$)。**结论** OSAHS患者白日嗜睡和认知功能障碍密切相关,不论重度还是轻中度OSAHS合并EDS较不合并EDS患者MoCA评分较低,且注意力缺陷最为明显。所以应早期识别OSAHS患者认知障碍,及时予以干预如持续气道正压通气,避免认知功能进一步恶化。

【关键词】 阻塞性睡眠呼吸暂停低通气综合征;白日嗜睡;认知障碍

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Effect of excessive daytime sleepiness on cognitive impairment in patients with obstructive sleep apnea hypopnea syndrome

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【Abstract】 Objective To explore the influencing factors of cognitive impairment in patients with obstructive sleep apnea hypopnea syndrome (OSAHS). **Methods** Enrolled in the study were 175 OSAHS patients (96 severe and 79 mild to moderate) diagnosed by polysomnography in the Sleep Center of Respiratory Department of Nanjing First Hospital from January 2018 to December 2019. According to the Epworth Sleepiness Scale (ESS) score and sleepiness symptoms, the patients were divided into OSAHS patients with excessive daytime sleepiness (EDS) and patients without EDS. The general information was collected, and the Montreal Cognitive Assessment (MoCA) was used to evaluate the cognitive impairment of the patients. OSAHS patients with and without EDS were compared in the cognitive impairment scores, and the related factors were analyzed. SPSS statistics 22.0 was used for statistical analysis. Comparison between the two groups was performed using t test or χ^2 test depending on data type. Correlation analysis was performed using Pearson test. Multivariate regression analysis was used to evaluate the factors related to MoCA and ESS. **Results** Oxygen desaturation index (ODI), lowest nocturnal oxygen saturation ($LSaO_2$) and percentage of total sleep time with oxygen saturation <90% (TS90%) were significantly different between severe OSAHS patients with and without EDS ($P<0.05$). Oxygen desaturation index

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(ODI) and TS90% in mild to moderate OSAHS patient with EDS were higher than those without EDS ($P<0.05$). Visual spatial executive ability, attention, delayed memory, abstract ability and orientation ability in the severe OSAHS patients were lower than mild to moderate OSAHS patients($P<0.05$). In severe OSAHS patients, MoCA in patients with EDS was lower than that in patients without EDS, and there was significant differences in attention and delayed memory($P<0.05$). MoCA in mild to moderate OSAHS patients with EDS was lower than that of patients without EDS, and difference with statistical significance was only seen with attention ($P<0.05$). MoCA was found to be negatively correlated to ESS, AHI, ODI and TS90% but positively to $LSaO_2$, the differences being statistically significant ($r=-0.432$, -0.511, -0.539, -0.420、0.458) ($P<0.01$ for all). ESS was positively correlated with body mass index, abdominal circumference, waist-to-hip ratio, ODI and TS90%, and negatively with $LSaO_2$, the differences being statistically significant ($r=0.262$, 0.299, 0.460, 0.538, 0.498, -0.417) ($P<0.05$ for all). Multivariate linear regression analysis showed that MoCA was independently correlated with ESS and ODI ($R^2=0.325$, $P<0.05$). **Conclusion** EDS is closely related to cognitive impairment in OSAHS patients. MoCA is lower in severe OSAHS patients or mild to moderate OSAHS patients with EDS than that of patients without EDS, and attention deficit is the most obvious. Therefore, early identification of cognitive impairment early intervention such as CPAP in the OSAHS patients can avoid further deterioration of cognitive function.

【Key words】 obstructive sleep apnea hypopnea syndrome; excessive daytime sleepiness; cognitive impairment

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阻塞性睡眠呼吸暂停低通气综合征(obstructive sleep apnea hypopnea syndrome,OSAHS)是最常见的睡眠呼吸疾病之一。OSAHS 主要发病机制是因为上气道反复塌陷导致慢性间歇性缺氧,机体产生氧化应激及患者睡眠碎片化等,从而累及全身多个系统损害[1,2]。神经认知障碍是与 OSAHS 相关的主要并发症之一[3],白日嗜睡(excessive daytime sleepiness,EDS)是 OSAHS 主要的症状之一。有学者探讨睡眠障碍对社区老年人认知功能和抑郁症状的影响,并得出 EDS、抑郁症状和认知能力差之间存在显著相关性的结论[4]。影响认知障碍的因素很多,EDS 是可能的因素之一。本研究通过探讨伴或不伴有 EDS 的 OSAHS 患者临床特征、认知障碍的程度及相关因素,进一步探讨引起认知障碍的原因,以便早期进行诊断及干预。

1 对象与方法

1.1 研究对象

本研究选择 2018 年 1 月至 2019 年 12 月于南京市第一医院呼吸科睡眠中心经多导睡眠监测诊断为 OSAHS 的患者 175 例。OSAHS 诊断符合 2011 年中华医学会颁布的诊断标准[5]。EDS 诊断标准:患者白天有自觉嗜睡症状,同时根据 Epworth 嗜睡量表(Epworth Sleepiness Scale,ESS)评分>9 分[6];未合并 EDS:无白天嗜睡症状,且 ESS 评分≤9 分。175 例患者重度 OSAHS 患者 96 例,轻中度 79 例。将重度及轻中度 OSAHS 患者分为合并 EDS 患者和未合并 EDS 患者。

纳入标准:(1)所有患者知情同意且依从性好;(2)患者不存在意识、视、听、读及写等障碍;(3)无严重心肝肾等器官功能不全;(4)入组前 3 个月未接受任何影响认知功能的相关药物治疗。排除标准:(1)滥用精神药物;(2)伴有心肝肾等严重疾病或者其他精神疾病及重大精神创伤史等;(3)无法完成测评;(4)受教育年限<9 年。本研究征得南京医科大学附属南京医院·南京市第一医院伦理委员会批准。

1.2 方法

测定和计算方法参考世界卫生组织标准和国内规范[7];每位患者睡眠监测当天采用蒙特利尔认知评估量表(Montreal cognitive assessment,MoCA)评价认知功能,内容包括视空间执行力(5 分)、命名力(3 分)、注意力(3 分)、语言能力(3 分)、抽象力(2 分)、计算能力(3 分)、延迟记忆力(5 分)及定向力(6 分)8 个维度方面的评价,受教育年限≤12 年加 1 分校正偏差;MoCA 量表评分为 0~30 分,正常值≥26 分,MoCA 评分<26 分判定为存在认知功能障碍[8]。MoCA 量表由 2 名经过专业培训的人员共同操作,评估之前对患者仔细解释,在患者充分理解量表内容基础上,单独并一次性完成。

多导睡眠监测(polysomnography,PSG)进行连续的同步记录至少 7 h,记录患者呼吸暂停低通气指数(apnea hypopnea index,AHI)、最低脉氧饱和度(lowest nocturnal oxygen saturation,$LSaO_2$)、氧减指数(oxygen desaturation index,ODI)和脉氧饱和度<90%时间占总睡眠时间百分比(percentage of total sleep time with oxygen saturation<90%,TS90%)。

1.3 统计学处理

采用 SPSS 22.0 统计软件进行数据分析。计量资料用均值±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验;计数资料用例数(百分率)表示,采用 χ^2 检验。采用 Pearson 进行相关性分析。应用多因素回归分析评价 MoCA 和 ESS 相关因素。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 重度和轻中度 OSAHS 患者中合并 EDS 和不合并 EDS 患者一般资料比较

重度和轻中度 OSAHS 患者中合并 EDS 和不合并 EDS 患者年龄、性别、合并症及受教育年限比较，差异均无统计学意义（均 $P>0.05$）。重度 OSAHS 合并 EDS 与不合并 EDS 患者体质量指数（body mass index，BMI）、腹围及腰臀比比较，差异均有统计学意义（均 $P<0.05$）；而轻中度 OSAHS 合并 EDS 和未合并 EDS 患者以上指标差异均无统计学意义（表 1）。

2.2 轻中度和重度 OSAHS 患者中合并 EDS 和未合并 EDS 患者睡眠参数比较

重度 OSAHS 合并 EDS 和不合并 EDS 患者 $LSaO_2$、ODI 和 TS90%比较，差异均有统计学意义（均 $P<0.05$）。轻中度合并 EDS 和未合并 EDS 患者 ODI 和 TS90%比较，差异均有统计学意义（均 $P<0.05$）。其余指标比较，差异均无统计学意义（表 2）。

2.3 轻中度和重度 OSAHS 患者中合并 EDS 和未合并 EDS 患者认知障碍评分比较

重度与轻中度 OSAHS 患者视空间执行力、注意力、延迟回忆、抽象能力、定向力及 MoCA 评分差异均有统计学意义（均 $P<0.001$）；重度及轻中度 OSAHS 合并 EDS 较未合并 EDS 患者 MoCA 评分更低，差异有统计学意义（均 $P<0.05$），其中重度伴 EDS 较不伴 EDS 者注意力及延迟回忆有统计学意义（均 $P<0.05$）；而轻中度合并 EDS 和未合并 EDS 患者仅注意力差异有统计学意义（$P<0.05$；表 3）。

表 1 轻中度和重度 OSAHS 患者中合并 EDS 和不合并 EDS 患者一般资料比较

Table 1 Comparison of baseline data between mild to moderate OSAHS and severe OSAHS patients with and without EDS

Item	Severe OSAHS patients ($n=96$)		Mild to moderate OSAHS patients ($n=79$)	
	Patients with EDS ($n=71$)	Patients without EDS ($n=25$)	Patients with EDS ($n=31$)	Patients without EDS ($n=48$)
Age (years, $\bar{x}\pm s$)	50.58±15.48	53.04±12.5	53.80±15.21	54.00±14.92
Male [n (%)]	66 (93.0)	21 (84.0)	24 (77.4)	31 (64.6)
Hypertension [n (%)]	42 (59.2)	13 (52.0)	17 (54.8)	28 (58.3)
CHD [n (%)]	31 (43.7)	9 (36.0)	10 (32.3)	12 (25.0)
Diabetes mellitus [n (%)]	8 (39.4)	9 (36.0)	10 (32.3)	15 (31.3)
Education level (years, $\bar{x}\pm s$)	12.83±3.16	13.00±3.46	13.84±3.00	12.96±2.95
BMI (kg/m^2, $\bar{x}\pm s$)	32.09±3.90 *	29.54±4.34	25.87±2.86	27.51±4.98
NC (cm, $\bar{x}\pm s$)	42.11±4.34	40.96±3.33	39.67±2.91	39.02±3.07
AC (cm, $\bar{x}\pm s$)	100.17±14.28 *	94.24±7.74	95.03±7.10	91.23±9.27
WHR ($\bar{x}\pm s$)	1.02±0.04 **	0.99±0.20	0.98±0.20	0.96±0.35

OSAHS: obstructive sleep apnea hypopnea syndrome; EDS: excessive daytime sleepiness; CHD: coronary heart disease; BMI: body mass index; NC: neck circumference; AC: abdominal circumference; WHR: waist hip ratio. Compared with severe OSAHS patients without EDS, *$P<0.05$; **$P<0.01$.

表 2 轻中度和重度 OSAHS 患者中合并 EDS 和未合并 EDS 患者睡眠参数比较

Table 2 Comparison of sleep parameters between mild to moderate OSAHS and severe OSAHS patients with and without EDS ($\bar{x}\pm s$)

Group	n	AHI (times/h)	$LSaO_2$ (%)	ODI (times/h)	TS90% (%)
Severe OSAHS	96				
With EDS	71	49.02±16.99	64.23±8.83 *	48.03±12.93 *	32.95±16.84 *
Without EDS	25	47.50±14.64	68.76±9.11	42.93±7.40	25.47±9.01
Mild to moderate OSAHS	79				
With EDS	31	20.59±4.17	78.35±7.36	20.10±6.98 ##	12.98±6.72 #
Without EDS	48	15.1±5.97	81.40±6.15	11.74±4.89	6.50±8.13

OSAHS: obstructive sleep apnea hypopnea syndrome; EDS: excessive daytime sleepiness; AHI: apnea hypopnea index; $LSaO_2$: lowest nocturnal oxygen saturation; ODI: oxygen desaturation index; TS90%: percentage of total sleep time with oxygen saturation<90%. Compared with severe OSAHS patients without EDS, *$P<0.05$; compared with mild to moderate OSAHS patients without EDS, #$P<0.05$; ##$P<0.01$.

表3 轻中度和重度OSAHS患者中合并EDS和未合并EDS患者认知障碍比较

Table 3 Comparison of cognitive impairment between mild to moderate OSAHS patients and severe OSAHS patients with and without EDS (points, $\bar{x}\pm s$)

Group	n	Visuospatial execution	Name	Attention	Language	Abstract ability	Calculation	Delayed memory	Orientation	MoCA
Severe OSAHS	96	3.59±0.84*	2.89±0.39	1.89±0.48*	2.30±0.55	1.69±0.47*	2.66±0.52	3.51±0.73*	5.18±0.77*	23.46±2.02*
With EDS	71	3.58±0.73	2.80±0.40	1.82±0.46#	2.15±0.58	1.66±0.48	2.65±0.51	3.42±0.73#	5.14±0.76	23.20±2.03#
Without EDS	25	3.64±1.11	2.84±0.37	2.08±0.49	2.32±0.48	1.76±0.44	2.68±0.56	3.76±0.66	5.28±0.79	24.20±1.85
Mild to moderate OSAHS	79	4.42±0.65	2.95±0.22	2.34±0.62	2.38±0.51	1.92±0.27	2.80±0.40	4.09±0.68	5.51±0.64	26.42±1.94
With EDS	31	4.30±0.65	2.90±0.30	2.13±0.67△	2.39±0.56	1.90±0.30	2.90±0.30	3.94±0.73	5.35±0.80	25.6±2.29△
Without EDS	48	4.63±0.57	2.98±0.14	2.48±0.55	2.38±0.49	1.94±0.24	2.73±0.45	4.19±0.64	5.60±0.49	26.9±1.50

OSAHS: obstructive sleep apnea hypopnea syndrome; EDS: excessive daytime sleepiness. Compared with mild to moderate OSAHS patients, *P<0.05; compared with severe OSAHS patients without EDS, #P<0.05; compared with mild to moderate OSAHS patients without EDS, △P<0.05.

2.4 相关性分析

将MoCA评分和ESS评分、AHI、$LSaO_2$、ODI和TS90%进行单因素相关分析,结果显示MoCA评分和ESS、AHI、ODI、TS90%呈负相关,和$LSaO_2$呈正相关,差异均有统计学意义(均P<0.01;表4)。将ESS评分和BMI、颈围、腹围、腰臀比、AHI、$LSaO_2$、ODI及TS90%进行单因素相关分析,结果表明ESS评分和BMI、腹围、腰臀比、ODI及TS90%呈正相关,和$LSaO_2$呈负相关,差异均有统计学意义(均P<0.05;表5)。将MoCA评分和ESS、AHI、ODI、TS90%及$LSaO_2$进行多因素线性回归,结果表明,MoCA评分和ESS评分、ODI独立相关(R^2=0.325,P<0.05)。ESS作为因变量,BMI、颈围、腹围、腰臀比、AHI、ODI、TS90%和$LSaO_2$作为自变量回归分析显示,ESS评分和腰臀比、ODI独立相关(R^2=0.352,P<0.05)。

表4 MoCA评分和ESS评分及睡眠监测指标相关性分析

Table 4 Correlation analysis between MoCA score and ESS score and sleep monitoring indexes of OSAHS patients

Item	r	P value
ESS	−0.432	<0.01
AHI	−0.511	<0.01
$LSaO_2$	0.458	<0.01
ODI	−0.539	<0.01
TS90%	−0.420	<0.01

MoCA: Montreal cognitive assessment; ESS: Epworth sleepiness scale; AHI: apnea hypopnea index; $LSaO_2$: lowest nocturnal oxygen saturation; ODI: oxygen desaturation index; TS90%: percentage of total sleep time with oxygen saturation<90%.

表5 ESS评分和OSAHS患者一般资料及睡眠监测指标相关性分析

Table 5 Correlation analysis between ESS and general data and sleep monitoring indexes of OSAHS patients

Item	r	P value
BMI	0.262	0.001
NC	0.579	0.055
AC	0.299	0.001
WHR	0.460	0.001
AHI	0.458	0.059
$LSaO_2$	−0.417	0.005
ODI	0.538	0.005
TS90%	0.498	0.001

BMI: body mass index; NC: neck circumference; AC: abdominal circumference; WHR: waist hip ratio; AHI: apnea hypopnea index; $LSaO_2$: lowest nocturnal oxygen saturation; ODI: oxygen desaturation index; TS90%: percentage of total sleep time with oxygen saturation<90%.

3 讨 论

认知功能包括注意力、记忆、执行功能、视觉空间、处理(认识)速度和语言能力等。OSAHS患者常常合并认知障碍,OSAHS患者的主要神经认知障碍通常存在于3个领域:(1)注意和警觉;(2)学习和记忆;(3)执行功能等[9]。有研究证实OSAHS患者认知功能障碍是患者疾病所致(OSAHS患者由于慢性间歇性缺氧导致氧化应激亢进,炎症因子增加,低氧/高碳酸血症等损伤大脑皮层或海马等导致大脑认知障碍[10]),但OSAHS是否存在其他影响认知障碍的因素,这是本研究重点探讨的部分。

Gabelle等[11]观察研究发现,嗜睡过度及较长时间卧床会增加体弱老年人认知能力下降的风险;我国也有学者通过抽样调查发现白天过多的嗜睡是认知能力下降的危险因素[4]。MoCA是一个用来对轻度认知功能异常进行快速筛查的评定工具,它评定了许多不同的认知领域。本研究发现重度OSAHS患者合并EDS和未合并EDS都存在轻度认知障碍,且合并EDS比不合并EDS患者认知障碍明显(P<0.05);而轻中度OSAHS患者合并EDS患者

同样存在认知障碍,而未合并 EDS 患者未发现有认知障碍;通过多因素回归分析也发现 MoCA 评分和 ESS 评分及 ODI 独立相关。既往研究也发现,反复呼吸暂停、睡眠碎片化、睡眠微觉醒和白天嗜睡与 OSAHS 患者的认知功能障碍有关[12,13]。本研究同时发现重度 OSAHS 患者合并 EDS 比不合并 EDS 患者注意力及延迟回忆受损更为明显;而轻中度 OSAHS 患者合并 EDS 与未合并 EDS 仅发现注意力有不同。Jester 等[14]通过研究发现,患有 EDS 的帕金森氏病患者在执行控制和处理速度方面存在认知缺陷,和本结果不一致。推测 EDS 不是一个完全独立影响患者认知障碍的因素,考虑还和合并的疾病有关。Angelelli 等[15]通过研究发现 OSA 患者在集中注意力和选择性注意力过程中均表现出不足,和本研究的最终结果一致。

本研究进一步探讨了 EDS 对 OSAHS 患者认知障碍产生的影响。国内学者盛颖等[16]通过临床观察性研究发现: EDS 与 AHI 呈正相关(r=0.249,P<0.001)。AHI 是判定 OSAHS 严重程度的重要指标,此研究显示 OSAHS 越重,日间嗜睡越明显。本研究发现重度 OSAHS 患者较轻中度 OSAHS 患者认知障碍更为显著;且发现 ESS 评分和 ODI 及 TS90%呈正相关,和 $LSaO_2$ 呈负相关,进一步印证 EDS 和低氧具有相关性。Kainulainen 等[17]通过研究证实严重的与睡眠有关的呼吸停止和饱和度下降对 EDS 的影响更大。睡眠破碎、呼吸事件和夜间缺氧可能是 EDS 的预测因素[18]。

本研究不仅发现低氧和 EDS 相关,还发现重度 OSAHS 伴 EDS 患者有更高的 BMI,更大的腹围及腰臀比,且 ESS 和腰臀比独立相关,与既往研究得出的结论一致[19,20]。推测可能是由于患者的 EDS 症状,活动量减少,加剧了中心型肥胖,导致腹围、腰臀比增加,脂肪堆积导致体质量上涨,进而 BMI 增加等;肥胖是 OSAHS 重要的发病因素之一,严重肥胖使 OSAHS 进一步加重,夜间缺氧及 EDS 更为严重,进而导致患者认知障碍等;EDS 除间接原因导致认知障碍外,不排除存在独立于以上因素的其他原因,如睡眠-觉醒周期的改变等,仍需进一步研究进行证实。

OSAHS 患者普遍接受的治疗方法是持续气道正压通气(continuous positive airway pressure, CPAP),CPAP 有助于防止上呼吸道阻塞,改善睡眠呼吸模式,纠正夜间低氧血症和 CO_2 潴留等。Zhou 等[21]总结了通过 CPAP 治疗 OSAHS 患者认知功能改善情况的文献,发现所有研究都表明 CPAP 治疗可以降低轻度和中重度 OSA 患者的 ESS 评分,改善患者主观白天嗜睡;应用 3~6 个月可以部分逆转患者神经认知功能。Bhat 等[22]通过研究也发现睡眠呼吸暂停患者在 CPAP 治疗期间情绪和认知功能得到改善。

本研究不足之处在于样本量偏小,导致研究结果有偏移的地方。另外,OSAHS 共病中如高血压和糖尿病等都和认知障碍有关联,虽然统计时这些基线资料在 2 组之间是平衡的,后续研究仍需尽量排除混杂因素;不同年龄段患者认知功能会有所不同,后续研究可以更加精细化,比如不同年龄段进行分层研究等。

综上,通过以上分析 OSAHS 患者 EDS 和认知功能障碍密切相关,不论重度还是轻中度 OSAHS 患者合并白日嗜睡患者 MoCA 评分较低,且注意力缺陷最为明显。所以早期识别 OSAHS 患者认知障碍,及时予以干预如 CPAP,避免认知功能进一步恶化导致永久性脑损伤,同时有助于提高生活质量及工作效率,减少交通事故的发生等。

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