医学影像物理

超声确定瑞舒伐他汀对老年冠心病左心室功能和血管内皮依赖性舒张功能

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【摘 要】目的：超声确定瑞舒伐他汀对老年冠状动脉粥样硬化性心脏病（CAHD）患者左心室功能、内皮依赖性舒张功能，同时测定血脂的变化。 方法：2014年1月至2014年12月收治的102例老年CAHD患者随机分为A组与B组，每组56例，并选取25例同期健康查体者作为对照组。A组为常规治疗，B组为常规治疗加连续8周口服瑞舒伐他汀（20 mg/d）。超声检测对入选对象的治疗前、治疗1、2、4和8周后测定左心室射血分数（LVEF）、左心室高峰充盈率（LVPFR）、内皮依赖性舒张功能（EDD）、非内皮依赖性舒张功能（NEDD），同时于治疗前和治疗4、8周后用酶法测定研究对象的总胆固醇（TC）、三酰甘油（TG）和高密度脂蛋白胆固醇（HDLC）。统计分析研究对象的检测结果，比较研究对象治疗前后各指标的变化。 结果：与正常对照组比较，治疗前A组和B组的左心室功能（LVEF和LVPFR）和内皮舒张功能（EDD和NEDD）指标均显著降低（P<0.05），而血脂水平则显著升高（P<0.01），但A组和B组之间各值均无统计学差异（P>0.05）。治疗2、4和8周后，A、B两组的 LVEF和LVPFR均较治疗前明显升高（P<0.05），但B组较A组升高更明显（P<0.05）。治疗2、4和8周后，A、B两组的EDD和NEDD均较治疗前有明显提高，但B组均较治疗前提高更明显（P<0.05）。老年CAHD患者的EDD、NEDD和LVEF均呈正相关（r=0.764,0.782；P<0.05）。治疗前两组患者血脂水平比较无统计学差异（P>0.05），治疗4和8周后，两组血脂水平均下降，但B组下降更为明显（P<0.01）。血管内皮舒张功能指标EDD升高与血脂TC、TG和HDLC降低之间呈负相关（r=-0.376,-0.412,-0.398；P<0.05）。 结论：老年CAHD患者血脂水平升高伴有左心室和血管内皮依赖性舒张功能改变，口服瑞舒伐他汀（20 mg/d）可改善这些功能并降低血脂。用瑞舒伐他汀改善老年CAHD患者左心血管功能和降低血脂是安全有效的。

【关键词】心脏彩色超声检测；冠状动脉粥样硬化性心脏病；瑞舒伐他汀；左心室功能；内皮舒张功能；降低血脂
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Applying ultrasonic detection for effects of rosuvastatin on left ventricular function and vascular endothelium dependent diastolic function of elderly patients with coronary heart disease

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Abstract: Objective To study on the effect of atorvastatin on left ventricular function and endothelium dependent diastolic function of elderly patients with coronary atherosclerotic heart disease (CAHD) by using ultrasonic detection, and measure the changes of blood lipids. **Methods** Admitted from Jan. 2014 to Dec. 2014, 102 elderly CAHD patients were randomly divided into group A and group B, each group of 56 patients. At the same period, 25 healthy persons were selected as control group. Group A was treated by routine treatment, while group B was treated with routine treatment and oral

administration of rosuvastatin (20 mg/d) for 8 weeks. Left ventricular ejection fraction (LVEF), left ventricular peak filling rate (LVPFR), endothelium dependent diastolic function (EDD) and non endothelium dependent diastolic function (NEDD) of patients and healthy persons were measured by ultrasonic detection in 0, 1, 2, 4 and 8 weeks after treatment. The total cholesterol (TC), triglyceride (TG) and high density lipoprotein cholesterol (HDLC) were measured by enzymatic way in 0, 4 and 8 weeks after treatment. The measured results were statistically analyzed, and the changes of indexes before and after treatment were compared. **Results** Before treatment, compared with the normal control group, left ventricular function (LVEF and LVEF) and endothelium dependent diastolic function (EDD and NEDD) were significantly decreased in the group A and group B ($P<0.05$), while the blood lipid levels were significantly increased ($P<0.01$), but no statistical differences were found between group A and group B ($P>0.05$). After 2, 4 and 8 weeks of treatment, LVPFR and LVEF in group A and group B were significantly higher than those before treatment ($P<0.05$), but the increase of group B was more significant than that of group A ($P<0.05$). After 2, 4 and 8 weeks of treatment, EDD and NEDD in group A and group B were significantly higher than those before treatment, but the increase of group B was more significant ($P<0.05$). EDD, NEDD of elderly CAHD patients were positively correlated with LVEF ($r=0.764, 0.782$; $P<0.05$). No significant differences were found in blood lipid between group A and group B before treatment ($P>0.05$); after 4 and 8 weeks of treatment, the blood lipids of group A and group B were decreased ($P<0.05$), but the decrease of group B was more significant ($P<0.01$). The increase of EDD was negatively correlated with the decrease of TC, TG and HDLC ($r =-0.376, -0.412, -0.398$; $P<0.05$). **Conclusion** The blood lipid level of elderly CAHD patients increases, with the changes of left ventricular function and vascular endothelium dependent diastolic function. Oral administration of rosuvastatin (20 mg/d) can improve these functions and lower blood lipids. The effect of rosuvastatin on improving left ventricular function and lowering blood lipids are effective and safe for elderly CAHD patients.

Key words: cardiac colour ultrasonic detection; coronary atherosclerotic heart disease; rosuvastatin; left ventricular function; endothelium diastolic function; reduce blood lipid

前　言

　　冠状动脉粥样硬化性心脏病（Coronary Athero-sclerotic Heart Disease, CAHD）发病的年轻化是医疗卫生健康的重要挑战之一，其对老年人健康安全的严重威胁也已受到全球关注，是WHO确定的第二号杀手[1-2]。CAHD 发病机制十分复杂，除与遗传因素有关外，也与饮食生活习惯密切相关。血脂升高引起的病理、生理改变是发病机制的重要直接因素，故早期诊断和预防十分重要。血管内皮功能失调是动脉粥样硬化病理过程中的一个早期改变，而浆胆固醇水平升高是动脉粥样硬化重要的独立危险因素，所以高胆固醇血症患者在动脉粥样硬化斑块形成前会出现血管内皮功能失调[1-3]，主要表现为内皮依赖性舒张功能障碍。心脏彩色超声检查是测定心脏功能的重要工具之一，CAHD早期一般无明显症状，但通过心脏超声检查即可发现心脏舒张功能和血管内皮细胞功能异常[3]。瑞舒伐他汀的药代动力学性质可抑制肝细胞内胆固醇合成从而降低细胞内胆固醇，使血脂浓度降低，从而改善CAHD功能，防止疾病进一步发展[4-5]。本文通过心脏彩超确定在瑞舒伐他汀治疗CAHD过程中，瑞舒伐他汀对CAHD患者左心室功能和内皮舒张功能的作用以及对血脂的影响，为临床治疗CAHD提供参考依据。

1　对象和方法

1.1　对象

　　选取 2014 年 1~12 月确诊、信息完整的 102 例住院CAHD患者，签署知情同意书后，用计算机选择的随机数字将患者分为常规治疗组（A组，$n=56$）和常规治疗+瑞舒伐他汀组（B组，$n=56$）。患者入选的诊断标准和排除标准均符合国家《CAHD诊断标准》（WS 319-2010）[6-7]，同时排除体检发现的严重糖尿病、其它心脑血管疾病或具有严重肝肾功能疾病患者。心脏病心功能分级标准评定采用美国纽约心脏病学会分级方案，患者包括心功能Ⅱ级 83 例，Ⅲ级 19 例。选取同一时期健康体检者 25 例作为对照。3 组研究对象的年龄、性别、体质量等基本资料见表 1，无统计学差异（$P>0.05$）。

1.2　用药方法

　　A组：常规治疗，给予常规改善循环、降血脂、血压控制、抗血小板凝集等基础治疗。B组：在 A 组常

表1 研究对象的一般情况 ($\bar{x} \pm s$)

Tab.1 General situation of patients and healthy persons (*Mean±SD*)

Group	*n* (M/F)	Age (Year)	Weight(kg)
A	25/26	62-84(68.58±8.76)	38-74(51.58±9.42)
B	27/24	61-87(69.48±9.96)	39-77(52.66±9.55)
Control	13/12	60-82(67.28±9.14)	41-73(51.17±9.02)

Group A: Rouitine treatment; Group B: Rouitine treatment trosuvastatin.

规治疗基础上,口服瑞舒伐他汀(Rosuvastatin Calcium,阿斯利康制药有限公司,批准文号:H20110563),每晚20 mg,连续用8周。研究对象于实验开始前2周停用其它他汀类药物,治疗期间严密观察患者的症状变化、不良反应和并发症情况。

1.3 彩超确定左心室功能和血管内皮舒张功能

彩超设备为Philips HD15高端智能彩超,采用探头为S8-3 Cardiac Probe,频率为5~10 MHz。A组和B组患者于入选的次日、治疗前和治疗1、2、4和8周后进行左心室功能和血管内皮舒张功能检测,对照组仅在体检时检测。研究对象左心室功能检测包括如下指标:(1)左心室射血分数(Left Ventricular Ejection Fraction, LVEF)和左心室高峰充盈率(Left Ventricular Peak Filling Rate, LVPFR)。将患者置于仰卧位,检测频率为25 MHz,记录的纸速50 nm/s,每例检测对象记录3个心动周期并求其均值。(2)肱动脉血管内皮依赖性舒张功能(Endothelium Dependent Dilation, EDD)。肱动脉内径变化可反映肱动脉内皮功能受损情况。7.0 MHz线阵探头, 探查深度4 cm, 同步记录心电图。整个测试过程中, 超声探头处于固定位置,血管内径测量每次均取同一部位。受试者仰卧位,暴露右上肢,探头置于肘上2 cm,于舒张末期测量静息状态下肱动脉内径(D_0),然后在前臂用血压计袖带加压至280 mmHg(1 mmHg=0.133 kPa),持续4 min后突然放松,在30~60 s内测定左心室舒张末期的肱动脉内径(D_1),即在血管舒张末期(同步ECG显示R波)时测量肱动脉前后内膜之间的距离,每次分别测3个心动周期,测定5次,取其平均值。EDD为肱动脉内径在加压(反应性充血)前后变化率,即EDD=$(D_1-D_0)/D_0 \times 100\%$。(3)肱动脉内皮非依赖性舒张功能(Non Endothelium Dependent Dilatation, NEDD)。EDD测试后,受试者体位同前,静息10 min,咽部喷入硝酸甘油喷雾剂(含量500 μg),5 min后测定肱动脉内径(D_2),测定5次,取其平均值。

NEDD为肱动脉内径在用硝酸甘油前后的变化率,即NEDD=$(D_1-D_0)/D_0 \times 100\%$。

血脂检测[6-7]选取的对照组仅在体检时空腹测定血脂1次。(1)用心脏彩超检测研究对象于治疗用药前、治疗4和8周后空腹12 h的血脂,清晨7:00抽取静脉血4 mL用做测定血脂标本。(2)血标本送达实验室后于3 h内室温下离心,分离血清并吸出转移至有盖的小试管中。当天未测定的血清置于-20℃中以备用于测定总胆固醇(Total Cholesterol, TC)或置于-70℃中以备用于测定三酰甘油(Triglyceride, TG)、高密度脂蛋白胆固醇(High Density Lipoprotein Cholesterol, HDLC),不可反复冻融以免影响测定结果。(3)血脂测定[6]采用美国Beckman公司生产的LX20全自动生化分析仪测定,TC、TG和HDLC试剂购自浙江伊利康生物技术有限公司,操作过程专人负责并专人核对,采用酶法测定TC、TG、HDLC。因低密度脂蛋白胆固醇(Low-Density Lipoprotein Cholesterol, LDLC)是利用Friedewald公式计算[6]所得结果,即:LDLC(mmol/L)=TC-(HDLC)-(TG/2.22),故本文未进行分析。用Landox质控血清质量,误差控制在批间≤9.8%,批内≤7.2%。

1.4 统计学方法

数据以均数±标准差表示,用SPSS13.0统计软件进行方差分析、*q*检验,同组对象治疗前后比较采用配对*t*检验。相关性分析采用Pearson检验,*P*<0.05为差异具有统计学意义。

2 结 果

2.1 治疗前左心室功能、血管内皮舒张功能和血脂水平变化

与正常对照组比较,治疗前A组和B组左心室功能(LVEF和LVPFR)和内皮舒张功能(EDD和NEDD)指标均显著降低(*P*<0.05),而血脂水平则显著升高(*P*<0.01),但A组和B组之间各值均无统计学

表2 A、B组和对照组治疗前左心室功能、内皮舒张功能(%)和血脂(mmol/L)检测结果($\bar{x} \pm s$)

Tab.2 Measured results of left ventricular function, endothelial diastolic function (%) and blood lipid (mmol/L) in group A, group B and control group before therapy (*Mean±SD*)

Group	*n*	LVEF	LVPFR	EDD	NEDD	TC	TG	HDLC
Control group	25	63.06±8.95	2.98±0.25	9.82±2.63	24.35±6.52	4.46±1.66	1.96±0.88	1.89±0.89
Group A	56	47.58±9.66[a]	1.94±0.45[a]	4.77±1.73[a]	18.82±4.81[a]	8.76±2.97[b]	4.26±1.76[b]	0.79±0.28[b]
Group B	56	48.27±9.85[a]	1.95±0.52[a]	4.66±1.91[a]	18.96±5.67[a]	8.89±2.81[b]	4.16±1.42[b]	0.87±0.32[b]
F value		4.824	5.278	5.018	4.612	8.816	7.618	6.264
P value		<0.05	<0.05	<0.05	<0.05	<0.01	<0.01	<0.01

Compared with control group, [a]$P<0.05$, [b]$P<0.01$.LVEF: Left ventricular ejection fraction; LVPFR: Left ventricular peak filling rate; EDD: Endothelium dependent dilation; NEDD: Non endothelium dependent dilatation; TC: Total cholesterol; TG: Triglyceride; HDLC: High density lipoprotein cholesterol

差异，数值详见表2($P>0.05$)。CAHD患者治疗前，彩色超声检查可见明显异常，见图1和图2。

2.2 A组和B组治疗后左心室功能和内皮舒张功能变化

治疗2、4和8周后，A、B两组LVEF和LVPFR均较治疗前明显升高($P<0.05$)，但B组较A组升高更明显($P<0.05$)，见表3。治疗2、4和8周后，A、B两组EDD和NEDD均较治疗前明显提高，但B组均较治疗前提高更明显($P<0.05$)，见表3。Pearson相关性分析结果表明，随着老年CAHD患者EDD和NEDD等内皮舒张功能指标的升高，其LVEF亦升高，老年CAHD患者EDD、NEDD和LVEF均呈正相关(r=0.764，0.782；$P<0.05$)。

2.3 血脂检测结果
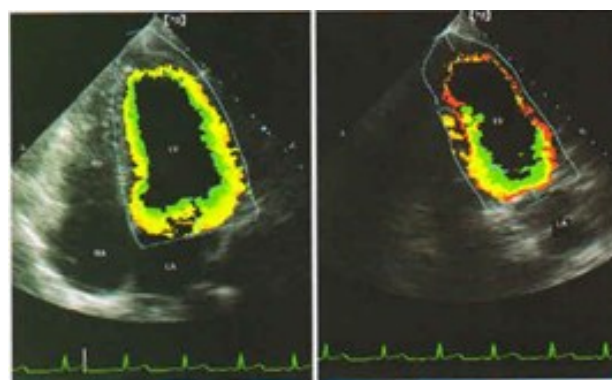
血脂升高评定依据参照《中国成人血脂异常防治指南》标准，治疗前两组患者血脂水平无统计学差异($P>0.05$)，治疗4周后，两组血脂均有下降，但B组下降更为明显，见表4($P<0.01$)。老年CAHD患者血脂数据通过Pearson相关性分析表明血管内皮舒张功能指标EDD升高与血脂TC、TG和HDLC降低呈负相关(r=-0.376, -0.412, -0.398；$P<0.05$)。

2.4 不良反应

治疗过程未见肝肾功能改变。A组发生头晕2例、轻度腹痛腹胀4例、便秘3例；B组发生头晕3例、皮肤轻度瘙痒1例、轻度腹痛腹胀5例、消化不良3例。上述症状经对症处理均于1周内消失，未影响治疗研究计划。

3 讨 论

近年来心血管疾病发病率的不断上升与人口老

a: Normal left ventricle   b: CHAD left ventricle

图1 左心室彩色室壁运动图

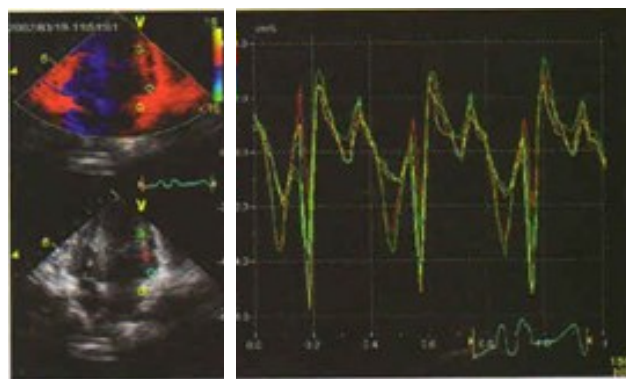Fig.1 Color kinesis image of left ventricle

图2 CAHD缺血状态时室壁运动速度分布（长轴方向）

Fig.2 Ventricular wall motion velocity distribution (long axis) of CAHD patients at ischemic state

Left: Ischemic area sampling; Right: Myocardium tissue velocity index of corresponding sample

龄化和生活方式的改变密切相关。老年心血管疾病中最常见的是CAHD，发病急而且病死率高，严重威

表3 A、B组患者治疗前后左心室功能和血管内皮功能变化(*n*=56, %, *x̄ ±s*)

Tab.3 Change of left ventricular function and vascular endothelial function before and after therapy (*n*=56, %, *Mean±SD*)

	Group	Before therapy	After therapy			
			1 week	2 weeks	4 weeks	8 weeks
LVEF	Group A	47.58±9.66	49.76±8.57	50.75±9.65 [a]	52.21±8.14 [a]	53.49±4.58 [a]
	Group B	48.27±9.85	53.55±8.75	59.26±8.72 [a]	62.45±2.21 [a]	63.92±2.42 [a]
	t/P value	0.378/>0.05	1.912/>0.05	3.087/<0.05	3.226/<0.05	3.434/<0.05
LVPFR	Group A	1.94±0.45	1.98 0.48	2.91±0.48 [a]	2.94±0.38 [a]	2.96±0.42 [a]
	Group B	1.95 ±0.52	1.99±0.55	3.98±0.53 [a]	3.99±0.56 [a]	4.17±0.76 [a]
	t/P value	0.412/>0.05	0.524/>0.05	2.845/<0.05	3.127/<0.05	3.624/<0.05
EDD	Group A	4.77±1.73	4.98±1.22	5.26±2.81 [a]	6.52±2.85 [a]	6.78±3.35 [a]
	Group B	4.66±1.91	4.97±1.47	6.94±2.92 [a]	7.94±3.17 [a]	8.82±4.92 [a]
	t/P value	0.408/>0.05	1.897/>0.05	3.842/<0.05	4.659/<0.05	4.981/<0.05
NEDD	Group A	18.82±4.81	19.61±3.78	19.65±4.62 [a]	19.79±4.88 [a]	19.82±5.38 [a]
	Group B	18.96±5.67	19.68±3.86	21.88±5.22 [a]	21.96±5.68 [a]	22.64±5.88 [a]
	t/P value	0.225/>0.05	1.326/>0.05	3.762/<0.05	3.894/<0.05	4.652/<0.05

Compared with the same group before therapy, [a]*P*<0.05.

表4 A组和B组治疗前后血脂变化(*n*=56, mmol/L, *x̄ ±s*)

Tab.4 Changes of blood lipids in group A and group B before and after therapy (*n*=56, mmol/L, *Mean±SD*)

Group		TC	TG	HDLC
Group A	Before therapy	8.76±2.97	4.26±1.76	0.79±0.28
	4 weeks after therapy	7.12±2.07[a]	3.28±1.62[a]	0.98±0.32
	8 weeks after therapy	6.82±2.87[a]	2.92±1.02[a]	1.28±0.52[a]
Group B	Before therapy	8.89±2.81	4.16±1.42	0.87±0.32
	4 weeks after therapy	6.12±2.17[b]	2.64±0.92[b]	1.18±0.42[b]
	8 weeks after therapy	5.42±2.72[b]	2.22±0.93[b]	1.38±0.54[b]

Compared with the data before therapy, group A: *t*=2.278~2.286, [a]*P*<0.05; group B: *t*=7.698~9.233, [b]*P*<0.01.

胁老年人健康与生命安全[7-9]。CAHD 发生与发展的直接诱因是冠状动脉血管因粥样硬化而发生循环故障、心肌供氧不足,或许是由局部血管痉挛引起心肌缺血甚至坏死性损伤。这类患者在疾病早期可能无临床症状,也可能出现心脏舒张功能异常,组织学和细胞学上表现为血管内皮功能改变。检测老年患者的心脏舒张功能和血管内皮功能状况可了解其疾病进展与预后,也可用于药物治疗效果评价[8-9]。

老年 CAHD 的发生与发展是多种因素综合作用的结果[1,10-12]。研究表明随年龄增长,心血管疾病伴高血脂的概率明显增加,遗传基因、激素水平降低所致的糖脂代谢紊乱或许成为其主因[3, 13-15]。利用他汀类药物瑞舒伐他汀的调节脂代谢作用和改善微循环作用,对降低高血脂、改善心室功能和调节血管内皮功能均具有良好作用[4, 16-18]。

他汀类药物是选择性羟甲基戊二酰辅酶 A(Hydroxymethylglutaryl Coenzyme A, HMG-CoA)还原酶抑制剂,主要在肝脏内竞争性抑制 HMG-CoA 还原酶还原 HMG-CoA,减少内源性胆固醇生成,对减少心血管疾病事件发生产生积极作用,同时上调肝细胞

表面 LDL 受体活性而加速 LDL 摄取和分解。瑞舒伐他汀是他汀类药物中效果最好的一种[5, 17-19]。研究表明他汀类药对冠心病患者冠脉内斑块炎症的多个环节均具有干预作用,可以稳定和缩小动脉粥样斑块,从而延缓动脉粥样硬化发生与发展[8, 20-22]。此外,他汀类药物还能改善内皮细胞功能、抑制平滑肌细胞增殖和聚集等[16-18]。

动脉粥样硬化作为 CAHD 的重要危险因素[19-22],而他汀类药物瑞舒伐他汀是抗动脉粥样硬化的有效药物,它的亲水性较强,且具有较强的肝脏特异性,是安全有效的降脂药物[25-27]。瑞舒伐他汀可通过降低血脂水平,减少动脉粥样硬化的发生,改善患者血管内皮舒张功能和左心室功能,促进患者的康复[28-30]。本研究显示老年 CAHD 患者存在左心室功能和血管内皮舒张功能改变,表现为 LVEF、LVPFR、EDD 和 NEDD 等指标降低。瑞舒伐他汀治疗 2 周后患者的这些指标均得到明显提高,随着治疗时间的延长,患者这些功能指标均逐步提高,表明瑞舒伐他汀对改善老年 CAHD 患者的左心室功能和血管内皮舒张功能有很好的效果,无明显不良反应。研究结果还表明患者左心室功能指标升高的同时血管内皮舒张功能亦升高,血管内皮舒张功能可能与其左心室功能相关,表现为 EDD、NEDD 和 LVEF 呈正相关,从而认为血管内皮舒张功能指标的变化也可以在一定程度上反应左心室功能变化[23-25]。

本研究表明老年 CAHD 患者血脂升高的同时左心室功能指标 LVEF 和 LVPFR,血管内皮舒张功能指标 EDD 和 NEDD 会降低。瑞舒伐他汀在降低血脂的同时可改善患者左心室和内皮舒张功能。笔者认为老年 CAHD 患者血脂水平升高伴有左心室和血管内皮依赖性舒张功能改变,口服瑞舒伐他汀(20 mg/d)可以改善这些功能和降低血脂[31-33],用瑞舒伐他汀改善老年 CAHD 患者左心血管功能和降低血脂是安全有效的。

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