

年轻人冠状动脉内膜增厚的形态定量研究*

赵红 赵培真 韩晓男 梁凤玲 杨方 杨瑞彪^① 武阳丰^② 张振声^① 唐金河^③

(中国医学科学院 中国协和医科大学 阜外心血管病医院病理研究室, ②流行病学研究室, 北京 100037)

Morphometric Study on Intimal Thickening of Coronary Arteries in Youth

ZHAO Hong, ZHAO Pei-Zhen, HAN Xiao-Nan, LIANG Feng-Ling, YANG Fang, YANG Rui-Biao, WU Yang-Feng, ZHANG Zhen-Sheng and TANG Jin-He

(Department of Pathology, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, ② Department of Epidemiology, Beijing 100037; ① Chinese Academy of Military Medical Sciences, Beijing 100850; ③ Institute of Criminal Science and Technology, Beijing 100007, China)

To investigate the relationship between the quantitative morphometric characteristics of intimal thickening and coronary atherosclerosis, 306 coronary arteries from 102 autopsied cases, 61 males and 41 females, aged 15 to 39 years (divided into 5 age groups), in Beijing were morphometrically studied.

Methods By using an image analysis system, intimal and medial thickness was measured, intimal to medial thickness ratio, eccentricity index, luminal stenosis rate, and average annual increasing rate in intimal thickness were calculated.

Results The intimal thickness increased with ageing. The intima was markedly thicker in males than in females of the same age group. Among the 3 coronary arteries [left anterior descending (LAD), right coronary (RC), and left circumflex (LC)] studied, the rate and

degree of intimal thickening were most marked in the LAD and then the RC and LC. Intimal thickening increased more rapidly in the LAD in both sexes in the 20~24 years group with average annual increasing rates of 8.6% (males) and 9.5% (females). The thickness then remained steady. However, a second peak of thickening of the LAD in the 35~39 years group in males with a average annual increasing rate of 9.2%, meanwhile the percentage of luminal stenosis was 57.4%. The average annual increasing rate of LAD was up to 3.8% in females in the 30 to 34 years group with no further increase in the 35~39 years group, but the percentage of luminal stenosis was <51%. Two different types of thickening, namely diffused and eccentric, were found, the latter with characteristic features of atherosclerosis is prone to develop into atherosclerosis plaque. The type of thickening of LAD which shows the highest prevalence of CHD clinically was eccentric.

Conclusions Intimal thickening with ageing is a changing from physiological to pathological process and intimal thickening forms the structural base for atherosclerosis.

KEY WORDS Intimal thickening; Coronary artery; Youth; Morphometry

摘要 为研究冠状动脉内膜增厚的年龄性改变及其与动脉粥样硬化发生发展的关系。应用 Quantimet 970 图像分析仪对北京地区 102 例意外死亡年轻人(15~39 岁)冠状动脉近侧端进行了形态定量及统计学处理。结果是,内膜增厚随年龄增长而增加,男厚于女,在同体三支冠脉的比较研究中内膜增厚的速度与程度均以左前降支居首位,依次为右冠状动脉和左旋支。两性 20~24 岁内膜增厚速度及平均年递增率较快,25~34 岁的十年间渐趋平稳,男性 35~39 岁及女性 30~34 岁再次出现增厚高峰,前者管腔狭窄率达 57.4%。内膜增厚的形态呈弥漫性和偏心性。本研究提示内膜增厚

* 本工作为国家“八·五”攻关课题“血管壁内皮细胞、平滑肌细胞与蛋白聚糖的相互关系在动脉粥样硬化斑块形成及消退中的作用”(85-915-03-04)中的一部分。

① 中国军事医学科学院 北京 100850.

③ 北京市刑事科学技术研究所 北京 100007.

的年龄性改变是从生理性向病理性发展的过程,是动脉粥样硬化形成的组织学基础,也为动脉粥样硬化和冠心病的预防及诊断提供了重要的形态学依据。

关键词 内膜增厚; 冠状动脉; 年轻人; 形态定量研究

冠状动脉(冠脉)粥样硬化(atherosclerosis, As)早期病变始发于少数婴幼儿,进展于青年期^[1~4],在中年或稍后可导致冠心病(coronary heart disease, CHD),危害极大。研究年轻人As为预测CHD的发生有重要意义。我国CHD虽较西方国家少,但有增多趋势^[5]。北京是As和CHD高发区^[6],因此,本文收集北京地区年轻人冠脉,在光镜观察基础上,采用图象分析仪对内、中膜进行定量分析,以期揭示冠脉内膜增厚与As发生发展的关系,为防治提供形态学依据。

1 材料和方法

1.1 材料

为能准确进行自体冠脉内膜数据的比较,在我们收集的北京地区1991~1993年意外死亡年轻人(15~39岁)的标本中选取三支血管均具备的心脏102例(男61例、女41例,男:女≈1.5:1)冠脉306支:左前降支(left anterior descending, LAD)、左旋支(left circumflex, LC)及右冠状动脉(right coronary, RC)各102支,按年龄、性别分成10组,组距5岁(Table 1)。

Table 1. Age and sex distributions of 102 youths (aged 15~39 yrs) of Beijing.

Age	male	female	total
15~	5	7	12
20~	20	9	29
25~	14	11	25
30~	10	6	16
35~	12	8	20
total	61	41	102

Note: from each of the 102 subjects 3 coronary arteries (LAD, LC and RC) were taken.

1.2 标本制备

将死后48h以内的心脏标本,按血流方向剖开,中性福尔马林原位固定一周后取材,LAD、LC及RC分别取自近侧端(不包括分支口),每段长5mm,石蜡

包埋,切片厚度4μm,HE及ET染色。

1.3 形态定量参数

用图象分析仪(Quantiment 970)对每张ET染色的冠脉横截面切片测量内、中膜(最大、最小及平均)厚度并计算内/中膜平均厚度比值,测量内膜面积、中膜面积及管腔面积;根据内膜平均厚度最小值(A)与最大值(B)的比值,求出偏心指数(EI)^[7], $EI \geq 0.5$ 为弥漫性增厚, <0.5 为偏心性增厚(Figure 1);管腔狭窄率是以内膜面积/(内膜面积+管腔面积) $\times 100\%$,比值 $\geq 51\%$ 为管腔狭窄。整个过程均用仪器的Quips软件编程,人机对话方式。

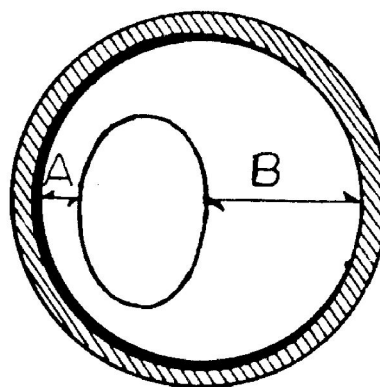


Figure 1. Eccentric index ($EI = A/B$). $EI < 0.5$, eccentric thickening; ≥ 0.5 , diffused thickening (from 本江 纯子, 心血管, 1992, 7, 652~659).

1.4 统计方法

图象分析所测各组数据用SPSS/PC软件进行统计学处理,经分析发现内膜厚度和内中膜厚度比值呈负偏态分布,经自然对数转换后接近正态分布,因此本文中所作各项统计分析均经对数转换后进行,文中描述的均值均为对数均值的反对数。管腔狭窄率接近正态分布,为直观起见,未作任何转换。组间均值的比较均为采用协方差分析和多组间两两均值比较的t检验。并计算了内膜增厚的平均年递增率。

2 结果

2.1 冠脉内膜增厚与年龄、性别

Table 2和Table 3所示北京地区年轻人15~19岁三支血管平均内膜厚度已为中膜的0.9倍,其中男性LAD达1.2倍,随年龄增长内膜增厚;35~39岁组内/中膜厚度比值平均为1.4倍,男性LAD达2.3倍。三支血管内膜平均厚度35~39岁组与15~19岁组相比,男性为2.3倍,女性为1.5倍。男性内膜增厚的速度及幅度均快于高于女性,内膜厚度男女性相

Table 2. Relationship between mean of natural logarithm of intimal thickness of coronary arteries and age, sex in youth(15~39 yrs) of Beijing($\bar{x} \pm s$).

Age	LAD		LC		RC	
	male	female	male	female	male	female
15~	-1.85 (157.24) ± 0.47	-2.13 (118.84) ± 0.47	-2.56 (77.30) ± 0.58	-2.39 (91.63) ± 0.61	-1.96 (140.86) ± 0.45	-2.29 (101.27) ± 0.57
20~	-1.51 (220.91) ± 0.57	-1.63 (195.93) ± 0.30	-1.95 (142.27) ± 0.58	-2.01 (133.99) ± 0.62	-1.72 (179.07) ± 0.33	-1.92 (146.61) ± 0.32
25~	-1.32 (267.14) ± 0.34	-1.73 (177.28) ± 0.33	-1.76 (172.04) ± 0.58	-2.06 (127.45) ± 0.62	-1.58 (205.98) ± 0.33	-1.73 (177.28) ± 0.32
30~	-1.47 (229.93) ± 0.23	-1.57 (208.05) ± 0.47	-1.77 (170.33) ± 0.63	-1.68 (186.37) ± 0.59	-1.74 (175.52) ± 0.45	-1.62 (197.90) ± 0.70
35~	-1.05 (349.94) ± 0.33	-1.72 (179.07) ± 0.59	-1.41 (244.14) ± 0.32	-2.00 (135.34) ± 0.52	-1.34 (261.85) ± 0.41	-1.81 (163.65) ± 0.39
total	-1.40 (246.60) ± 0.47	-1.75 (173.77) ± 0.45	-1.82 (162.03) ± 0.60	-2.04 (130.03) ± 0.55	-1.63* (195.93) ± 0.48	-1.87* (154.12) ± 0.52

* $P < 0.01$, vs the corresponding coronary artery of male, by the analysis of coariance to control age factor, * means the same in the other tables. # $P < 0.01$, vs LAD of the same sex, by analysis of covariance to control age factor, # means the same in the other tables. Note: Figures in brackets represent in⁻¹ of mean $\times 1000(\mu\text{m})$ and mean the same in the other tables.

Table 3. Relationship between mean of natural logarithm of the ratio of intimal to media thickness and age, sex in youth(15~39 yrs) of Beijing($\bar{x} \pm s$).

Age	LAD		LC		RC	
	male	female	male	female	male	female
15~	-0.21 (1.23) ± 0.64	-0.50 (0.95) ± 0.50	-0.17 (0.84) ± 0.72	-0.04 (0.67) ± 0.57	-0.04 (0.67) ± 0.58	-0.20 (0.82) ± 0.70
20~	0.37 (1.45) ± 0.57	0.29 (1.34) ± 0.37	0.10 (1.11) ± 0.45	0.02 (1.02) ± 0.36	0.14 (1.15) ± 0.57	-0.05 (0.95) ± 0.44
25~	0.55 (1.73) ± 0.41	0.35 (1.42) ± 0.37	0.13 (1.14) ± 0.50	0.11 (1.12) ± 0.35	0.24 (1.27) ± 0.43	0.27 (1.31) ± 0.37
30~	0.41 (1.51) ± 0.25	0.39 (1.48) ± 0.56	0.34 (1.40) ± 0.49	0.18 (1.20) ± 0.62	0.09 (1.09) ± 0.41	0.44 (1.55) ± 0.74
35~	0.81 (2.25) ± 0.48	0.31 (1.36) ± 0.42	± 0.44 (1.55) ± 0.32	0.01 (1.01) ± 0.48	0.29 (1.34) ± 0.49	-0.02 (0.98) ± 0.54
total	0.49 (1.63) ± 0.50	0.26* (1.30) ± 0.44	0.19 (1.21) ± 0.49	0.06 (1.06) ± 0.45	10.17* (1.19) ± 0.49	0.09 (1.09) ± 0.56

比差异显著($P < 0.01$)。两性在 20~24 岁增厚速度较快,女性 30~34 岁及男性 35~39 岁再次出现增厚高峰,这三个年龄组内膜均明显厚

于前一年龄组($P < 0.01$)。20~29 岁各组内膜与 15~19 岁相比增厚明显($P < 0.01$);男性 25~34 岁的两个年龄组内膜增厚较缓慢,两组间

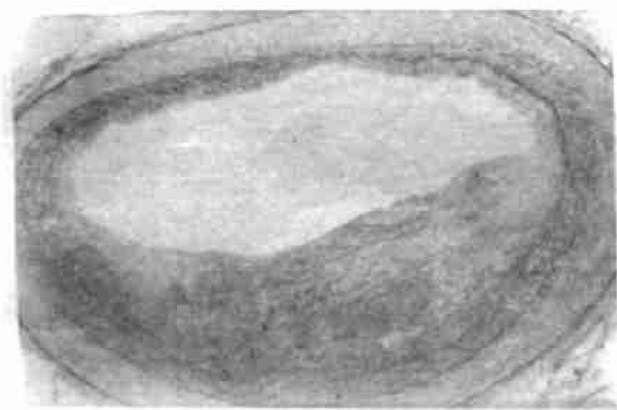


Figure 2. Intimal eccentric thickening of LAD.
EI<0.5 (a male peasant, 36 yrs), ET×24

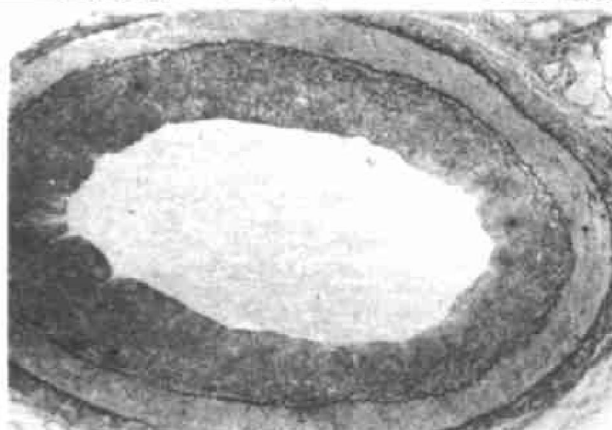


Figure 3. Intimal diffused thickening of RC.
EI>0.5 (a male peasant, 31 yrs), ET×18.

Table 4. Relationship between eccentric index and mean of natural logarithm of intimal thickness in youth (15~39 yrs) of Beijing ($\bar{x} \pm s$).

	Eccentric index (EI)			Intimal thickness
	male	female	male+female	male+female
LAD	0.42 ± 0.17	0.44 ± 0.14	0.43 ± 0.16	$-1.54(214.38) \pm 0.49$
LC	0.69 ± 2.05	0.41 ± 0.19	0.58 ± 1.59	$-1.91(148.08) \pm 0.59$
RC	0.44 ± 0.15	0.57 ± 0.17	0.50 ± 0.17	$-1.73(177.28) \pm 0.51$

Note: EI=A (Intimal thickness)/B (Intimal thickness); EI>0.5, diffused thickening, EI<0.5, eccentric thickening.

Table 5. Age and sex distribution of percentage of luminal stenosis in youth (15~39 yrs) of Beijing.

Age	LAD		LC		RC	
	male	female	male	female	male	female
15~	41.0 ± 16.3	35.6 ± 8.2	31.8 ± 16.1	46.7 ± 15.5	39.9 ± 7.7	32.9 ± 11.4
20~	49.0 ± 17.0	40.5 ± 7.4	40.7 ± 12.4	39.3 ± 11.0	45.9 ± 17.1	38.5 ± 14.4
25~	50.6 ± 9.6	45.8 ± 14.8	48.1 ± 12.0	40.4 ± 9.4	45.7 ± 13.8	45.0 ± 12.8
30~	48.2 ± 10.6	41.8 ± 11.7	47.2 ± 15.6	40.1 ± 12.9	42.0 ± 8.8	46.5 ± 18.0
35~	57.4 ± 12.2	47.6 ± 8.0	48.4 ± 9.1	42.8 ± 11.7	50.3 ± 16.9	45.0 ± 14.8
total	50.2 ± 13.9	$42.6 \pm 11.0^*$	$44.3 \pm 13.2^*$	$41.7 \pm 11.6^*$	$45.6 \pm 14.5^*$	$41.7 \pm 14.3^*$

Note: Percentage of luminal stenosis=intimal area/(intimal area+luminal area)×100%, ≥51%, luminal stenosis.

内膜厚度比较差异不显著($P>0.05$);男性 30~34 岁及女性 35~39 岁内膜厚度与前一年龄组相比略有减轻。

2.2 冠脉内膜增厚与部位

由 Table 4 看出,在控制年龄、性别因素之后,三支血管中,内膜厚度以 LAD 最显著,RC 次之,LC 最轻,LAD 与 LC、RC 相比差异非常显著($P<0.01$)。

2.3 内膜增厚的形态特点

本组 EI(Table 4),男性偏心性增厚重于女

性($P<0.01$),LAD 的 EI=0.43 为偏心性 (Figure 2),LC 及 RC 的 EI≥0.5 系弥漫性 (Figure 3),LAD 与 RC、LC 相比差异非常显著($P<0.01$)。

2.4 管腔狭窄率与年龄、性别及部位

根据 Table 5 管腔狭窄率随年龄增长而增加,男高于女($P<0.01$),三支血管相比,LAD 狭窄率最高($P<0.01$),依次为 EC 及 LC,35~39 岁男性 LAD 管腔狭窄率为 57.4%。

3 讨论

3.1 冠脉内膜增厚与年龄及动脉粥样硬化病变的关系

动脉粥样硬化病变的形成是一个多因素参与的复杂过程,而最早出现的改变为内膜增厚。内膜增厚部位与 As 病变相一致^[8],已有作者把婴幼儿及儿童期冠脉内膜增厚作为 CHD 危险因素的一项指标^[9],并有研究资料证明冠脉内膜增厚与年龄增长有一定的相关性^[2,10]。研究靶人群冠脉 As 应研究内膜增厚的一些形态特征。从北京地区 15~39 岁连续性年龄组的测量结果,两性内膜增厚高峰的 4 个年龄组(男 20~24 岁,35~39 岁;女 20~24 岁,30~34 岁)其内膜厚度平均可为本组前一年龄组的 1.4 倍,其中 LAD 内膜增厚平均年递增率 4 组依次为 7.0%、8.8%、10.5%、3.3%。根据内/中膜厚度比值明显增大,其原因主要是内膜增厚而中膜无明显变化,内膜随年龄增长而增厚从本研究中得到肯定。而某些年龄组(男 25~29 岁)内膜增厚缓慢或稍有减轻(男 30~34 岁,女 35~39 岁),提示在内膜增厚过程中可能存在影响内膜增厚速度或限制增厚甚至逆转的因素,有待进一步研究。从本组 As 病变检出结果(另文报告),与内膜增厚相比,二者的年龄、性别分布及内膜增厚部位与 As 病变发生均相一致。已知人和很多实验动物的冠脉从出生起就有一个明显的内膜层^[11],尤其是冠脉近侧端及其血管分叉处,根据循环力学理论,血管分支前口血流处于低切变率的流动分离区和湍流区,血管分支后口具有较高的切应力,这些均可引起早期内膜增厚性改变,更可引起内皮损伤,血小板粘附导致血栓形成;影响低密度脂蛋白(low density lipoprotein, LDL)浸入内膜,产生胆固醇或其它积聚物质的跨血管转运,最终形成 As 病变。因为 LAD 受血流动力学影响较 EC、LC 为大,所以内膜增厚程度、As 病变检出率均居 3 支血管之首。由此得出,冠脉内膜增厚的年龄性改变是从生理性向病理性发展的过程,是 As 病变形成的组织学基础,从婴幼儿及儿童期起就应将其视为 CHD 的一项危险因素。

3.2 内膜增厚的形态、管腔狭窄与冠心病

以内膜面积占内膜面积与管腔面积之和的百分比评价管腔狭窄,认为能较真实、准确地反应实际狭窄程度。根据 Table 5 狭窄率的增长随年龄增加而增高,比较内膜增厚及狭窄率与年龄、性别与血管分布三者较为一致。同时发现,在内膜增厚最明显的 35~39 岁组男性 LAD 狭窄检出率及 As 病变检出率均较其它组为高,说明内膜增厚可导致 As 并进一步引起管腔狭窄,但本研究亦见男性 25~29 岁组狭窄检出率高于 30~34 岁组,而 As 病变检出率前者却低于后者,提示冠脉管腔狭窄并非全由 As 病变引起。本组冠脉内膜细胞核数、面密度测量数据揭示,在内膜增厚过程中,细胞核数、面密度随年龄增长而减少,15~19 岁组与 35~39 岁组相比差异非常显著($P < 0.01$)。认为内膜增厚无论是初期中膜平滑肌细胞(smooth muscle cell, SMC)迁移至内膜增殖或随后的间质增多均可成为管腔狭窄的组织学基础,因此即使在未形成明显的 As 病变前冠脉内膜增厚的年龄性改变亦可导致管腔狭窄。

从 Table 4 看到 LAD 呈典型偏心性增厚。血流动力学理论认为动脉内只要在分流体顶端存在细小突出(甚至小于 1 mm)就会在分流体下游主管壁附近产生另外的小分离区^[12],引起血流停滞或逆流或发生涡流及湍流等,内皮缺氧而受损,启动 As 病变形成的一系列因素。根据这一理论,偏心性增厚比弥漫性增厚更易形成 As,后者虽有管腔内径的缩小,但因内膜增厚较均匀,与前者相比,对血流动力学影响相对较晚,推测 As 病变的形成较缓慢,发生时间较晚,病变程度较轻。本研究是在冠脉横截面组织学切片上进行测量并求出狭窄百分率,一旦内膜增厚,不论是偏心性还是弥漫性,内膜面积就会增大,因此在 As 形成前,这两种形态的增厚均有可能出现狭窄率增高甚至管腔狭窄,亦即都有可能造成心肌供血不足,这与临床医师冠脉造影时以管腔隆起性(偏心性)病变判断管腔狭窄不同。因此,对有冠脉缺血表现,而造影又未能发现隆起性病变的患者,临床医师应想到

内膜弥漫性增厚所致管腔狭窄缺血的可能性。

参考文献

- 1 动脉粥样硬化病理普查协作组. 7 159 例冠状动脉和 2 044 例主动脉粥样硬化病理普查总结. 中华病理学杂志, 1983, 12: 81~86.
- 2 Stary HC. The sequence of cell and matrix changes in atherosclerosis lesions of coronary arteries in the first forty years of life. *Eur Heart J*, 1990, 11(Suppl E): 3~19.
- 3 Pesonen E, Norio R, Hirvonen J, et al. Intimal thickening in the coronary arteries of infants and children as an indicator of risk factors for coronary heart disease. *Eur Heart J*, 1990, 11(Suppl E): 53~60.
- 4 Pathobiological determinants of atherosclerosis in youth research group. Natural history of aortic and coronary atherosclerotic lesions in youth. *Arterioscl Thromb*, 1993, 13: 1 291~98.
- 5 陶寿琪. 心血管病的预防. 见: 汤健, 丁金凤, 等编著: 心血管疾病. 北京医科大学 中国协和医科大学联合出版社. 1990; 1~4.
- 6 Zhao PZ, Deng ZL, Zhang ZS, et al. The influence of age and location of arterial lesion on the pathogenesis and development of early atherosclerotic lesions in youth. *Chin Med J*, 1994, 107: 171~175.
- 7 本江 纯子, 斋藤 颖, 森内 正人, et al. PTCA 後の病変形態から再狭窄の出現を予知するとは可能か? 心血管. 1992, 7 (6): 652~659.
- 8 Per Grottnum, Aud Svindland, Lars Walloe. Localization of atherosclerotic lesions in the bifurcation of the main left coronary artery. *Atherosclerosis*, 1983, 47: 55~62.
- 9 Pesonen E, Norio R, Hirvonen J, et al. Intimal thickening in the coronary arteries of infants and children as an indicator of risk factors for coronary heart disease. *Eur Heart J*, 1990, 11(Suppl E): 53~60.
- 10 Bierman EL, Ross R. Aging and atherosclerosis. In Paolett R and Gott AM(eds). *Atherosclerosis Reviews*. New York, Raven Press, 1977, 79~84.
- 11 Kim DN, Lee KJ, Schmee J, et al. Quantification of intimal cell masses and atherosclerotic lesions in coronary arteries of control and hyperlipidemic swine. *Atherosclerosis*, 1984, 52: 115~122.
- 12 王鸿儒. 血液循环力学. 北京: 北京医科大学 中国协和医科大学联合出版社, 1990, 196~210.

(本文 1994-11-20 收到, 1995-01-28 修回)

名词术语的汉英对照及缩写(I)

乙酰胆碱	acetylcholine, Ach
乙酰低密度脂蛋白	acetyl low density lipoprotein, ALDL
干扰素诱导蛋白	interferon-induced protein, IP
廿碳五烯酸	eicosapentaenoic acid, EPA
廿二碳六烯酸	docosahexaenoic acid, DHA
不饱和脂肪酸	unsaturated fatty acid, UFA
心肌梗塞	myocardial infarction, MI
牛主动脉内皮细胞	bovine aortic endothelial cell, BAEC
牛血清白蛋白	bovine serum albumin, BSA
右冠状动脉	right coronary, RC
左前降支	left anterior descending, LAD
左室射血分数	left ventricles ejective fraction, LVEF
左室射血时间	left ventricles ejective time, LVET
右室射血前期	left ventricles preejective period, LVPEP
左室收缩期末容积	left ventricles end-systolic volume, LVESV
左室舒张期末容积	left ventricles end-diastolic volume, LVEDV
去甲肾上腺素	noradrenaline, NA norepinephrine, NE

(胡必利编写)