Coronary atherosclerosis: Un-altered physiology

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Abstract

Background: End-stage coronary artery atherosclerosis has been studied extensively but the exact mechanisms of initiation and progression have not been defined fully. The aim of this study was to mathematically describe luminal change in relation to coronary vessel wall thickness in its progression from normal to atherosclerotic to establish whether these explain the pathophysiology.

Methods: One hundred coronary artery sections were graded histologically as ‘normal’ to ‘highly atherosclerotic’. Random systemic sampling by image analysis yielded 32 measurements (lumen radius and intima, medial, and adventitial thickness) from each section along 32 evenly spaced radii.

Results: The raw data follow an undulating course in relation to successive segments in all sections analyzed, pointing to a dynamic and well-ordered system. The calculated values, studied in triplets, followed a non-synchronized parabolic course, which was converted to linearity by taking the change in numbers ($n-(n-1)=\Delta$) into account. The course and sign of ‘ Δ vessel wall’ (resulting from summed Δ intima, Δ media, Δ adventitia) and ‘ Δ lumen radius’ values were unique for each triplet. Triplets order according to ‘ Δ lumen radius minus Δ vessel wall’ and its course given by the trendline a-value presented stages in which increased Δ vessel wall resulted in increased Δ lumen radius in stages 1 and 3 and decreased Δ lumen radius in stage 2. This phenomenon was found in all sections regardless of histological indication and independent of vessel wall constituent parts (intima, media, adventitia).

Conclusions: Similar basic processes are defined in all sections regardless of histological rating, indicating un-altered physiology. As such, coronary atherosclerosis can only be defined by a large to small shift of the triplets Δ vessel wall trendline a-value. Consequently,

36 no parameter of vessel wall pathology exists in absolute terms. Vessel wall composition has
 37 no importance for Δ lumen radius.

38 **Keywords:** coronary artery, atherosclerosis, image analysis, basic process, triplets course,
 39 semi-ranges

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Introduction

The anatomy and pathology of the coronary arteries are widely studied, especially by histological means. However, basic knowledge is lacking regarding, for example, the mechanism of arterial tapering, which corresponds to deficient knowledge of vessel wall/lumen interactions and, even more fundamentally, the intimal, medial, adventitial interplay.

Research has traditionally focused on the histopathology of plaque formation, the end-stage atherosclerotic process. The process from initiation to plaque formation has often been studied in a retrograde manner [1-3], which may lead to cause/effect reversal. An enlarged intima was considered a characteristic and regarded as a key player in atherosclerotic pathology [4, 5]. Consequently, the limits of normality, the thickness of the media and adventitia, and their role in atherosclerosis remain elusive.

We hypothesized that mathematical differences in the cross-sectional dimensions of normal and atherosclerotic arteries between stages could be used to help explain the pathophysiology of coronary artery atherosclerosis. This study aims to bridge the knowledge gap between the physiology of vessel morphology and the pathogenesis of atherosclerosis by mathematically defining both processes. Using a specially designed morphometric method termed ‘random systemic sampling’ [6], we aim to define how vessel wall thickness and lumen size are related and how the vessel wall layers (intima, media, adventitia) contribute to the pathophysiology of atherosclerosis.

Material and Methods

Study population and ethical approval

Study samples were obtained from autopsies of unselected patients regardless of the cause of death. No inclusion or exclusion criteria were applied. A total 100 cases were accepted and included for study. The Haaglanden MC ethics committee approved the study protocol and the use of specimens obtained from routine post-mortem examinations.

Coronary artery sampling and histology

Tissue blocks from the heart with coronary vessels attached were fixed by submersion in 4% phosphate-buffered formaldehyde solution (0.1M, pH 7.0) for 48 hours prior to further sampling. The arteries were not pressure perfused in order to retain ‘natural’ residual vascular wall stress. Vessel cross-sections were selected at random with no preference for left or right coronary arteries, sampling site, or cause of death. Sections were processed using routine methods, paraffin embedded, and 5- μ m sections cut and stained with hematoxylin and eosin for microscopic assessment. Morphometric assessment was preferentially performed on von Gieson/elastica stained sections.

Dataset

All sections were imaged and assessed by microscopy. Sections were histologically defined as follows: normal (intima < media), circumferential non-atherosclerotic enlarged vessel wall (intima $\geq$ media), circumferential and unilateral atherosclerotic enlarged vessel wall (signs of atherosclerosis, i.e., pattern of acellularity, cholesterol deposition, calcification, fibrosis, inflammation). Thus, all sections together represented the course from ‘normal’ (no signs of atherosclerosis) to ‘circumferential atherosclerosis’. One fully analyzed specimen from each histologically defined group highlighted the mathematical changes during progression. An additional section was histologically rated as ‘extreme unilateral atherosclerosis’ (not shown).

Image analysis

Computer-assisted image analysis was performed using ZEN 2 lite software (Carl Zeiss). Digitized tissue sections were displayed on a monitor and the center of each vessel located using a computerized best fit circle procedure. Only sections with an external elastic lamina Feret circle of at least 0.8 were used to exclude sectioning artefacts and interpretation bias. Using a random starting position, 32 radii were drawn from the center (i.e., one every 11.25 degrees) (random *systemic* sampling; Fig 1). The observer then identified and marked the positions of the endothelium, internal and external elastic lamina, and the adventitial-fat border along each radius. The lumen radius (Rlu) and the dimensions of the intima, media, and adventitia (INTd, MEDd, and ADVd, respectively) at each location were calculated in micrometers by the software. Matched values along each radius were jointly termed the ‘measurement unit’. Thirty-two measurement units were available for each section. All data were tabulated for further analysis.

Fig 1. Random systemic sampling computer-assisted image analysis.

The center point is located by the best fit circle procedure. Thirty-two radii differing by 11.25 degrees defined 32 measurement units of the lumen radius and intima, media, and adventitia dimensions.

Validation of the term value as a computerized classification parameter

INTd, MEDd, and ADVd were highly variable, even between two consecutive measurement units and regardless of the originating section. As the three vessel wall layer dimensions were not usually independent, they were defined as a single functional unit (FU-1). Similarly, Rlu-Wd, VWd, and Rlu defined a functional unit (FU-2). The relationship between the three values constituting FU-1 and FU-2 was parabolic and interrelated according to the formula $ax^2 + bx + c$. A constant characteristic of each functional unit (the ‘term value’; T-FU1 and T-

FU2) was produced by subtracting the difference between ADVd and MEDd from the difference between MEDd and INTd, and subtracting Rlu-VWd from VWd-(Rlu-VWd), respectively.

Process study

Data from random systemic sampling represented a *static* state, a snapshot in time. Each segment provided FU-1 and FU-2, which were characterized by T-FU1 and T-FU2, respectively. T-FU2 values set against consecutive segment numbers showed a well-ordered saw-toothed course in each section; the upward course changed to a downward course at an acute angle (Fig 2-5), indicating a *dynamic* process.

Fig 2. Section rated ‘normal’.

(A) Micrograph. (B) Scatter diagram T-FU2, Rlu-VWd, VWd, and Rlu vs. segment numbers. (C) T-FU1, INTd, MEDd, and ADVd vs. segment numbers.

Fig 3. Section rated ‘circumferential enlarged intima’.

(A) Micrograph. (B) Scatter diagram T-FU2, Rlu-VWd, VWd, and Rlu vs. segment numbers. (C) T-FU1, INTd, MEDd, and ADVd vs. segment numbers.

Fig 4. Section rated ‘unilateral atherosclerosis’.

(A) Micrograph. (B) Scatter diagram T-FU2, Rlu-VWd, VWd, and Rlu vs. segment numbers. (C) T-FU1, INTd, MEDd, and ADVd vs. segment numbers.

Fig 5. Section rated ‘circumferential atherosclerosis’.

(A) Micrograph. (B) Scatter diagram T-FU2, Rlu-VWd, VWd, and Rlu vs. segment numbers. (C) T-FU1, INTd, MEDd, and ADVd vs. segment numbers.

The changes in the INTd, MEDd, and ADVd and Rlu-VWd, VWd, and Rlu of consecutive segments were studied in triplets. Each triplet provided three successive values of FU-1 and FU-2 defined by their collective parabolic course and represented by their corresponding trendline formula ($R^2=1$). Intermediate segment values were calculated by interpolation. For example, triplet (1-3): segment numbers (x) and segment numbers squares (x^2) interpolated in formula $y=ax^2 + bx + c$ provided calculated y values of $x= 1; 1.1; 1.2; \dots 2; 2.1; \dots 3$. Therefore, each section provided 16 triplets (1-3), (3-5), ... (31-1), each consisting of 20 calculated FU-1 and FU-2 component values. The non-synchronized parabolic course of INTd, MEDd, and ADVd and Rlu-VWd, VWd, and Rlu in relation to T-FU1 and T-FU2, respectively, were marked by strong variability in peak/bottom parabola values, which made mutual comparisons impossible. Therefore, a step by step course was described by the value change (Δ values 1.1-1.0 ... n-(n-1)), which transformed the parabolic relationship into a linear one (trendline formula: $y = ax + b$, $R^2=1$).

Results

Measurement data

Measurement data for 'normal' (Table 1, Fig 2), 'circumferentially enlarged intima' (Table 2, Fig 3), 'unilateral atherosclerosis' (Table 3, Fig 4), and 'circumferential atherosclerosis' sections (Table 4, Fig 5) showed the saw-toothed course of T-FU2 in relation to segment number. The additional 'extreme unilateral atherosclerosis' section (not shown) also presented this phenomenon. T-FU2 curves were similar to Rlu-VWd curves, and to a lesser extent Rlu curves. The VWd and Rlu were generally antagonistic, but some segments followed a congruent course. An increase in the VWd was not always accompanied by a decrease in Rlu, and vice versa. The INTd, MEDd, and ADVd also alternated, but did not follow a distinct pattern.

Table 1. Measurement Values of 32 Segments in a ‘Normal’ Section.

Segment	T-FU2	Rlu-VWd	VWd	Rlu	T-FU1	INTd	MEDd	AVDd
1	181	143	105	248	-68	3	58	45
2	32	85	138	223	5	18	44	76
3	68	97	126	223	-109	7	79	41
4	-2	59	121	181	-34	13	52	57
5	-52	41	135	176	-6	13	47	75
6	-62	36	133	168	-7	13	47	74
7	-138	10	158	168	-6	6	55	97
8	-25	54	132	185	-17	10	50	72
9	-25	54	133	186	-14	13	49	71
10	-2	67	136	203	-17	9	51	76
11	-11	66	143	208	-69	13	70	59
12	72	97	123	220	-9	18	44	61
13	141	132	122	254	0	13	41	69
14	139	130	121	251	-28	11	50	60
15	150	134	119	253	-48	11	56	52
16	155	134	113	247	-49	7	54	52
17	124	128	131	259	-42	16	58	58
18	190	152	115	267	-22	20	46	49
19	133	129	126	256	-35	20	54	53
20	147	137	128	265	-27	16	52	60
21	62	100	138	238	-60	13	66	60
22	-30	62	154	216	-25	27	60	68
23	2	72	142	214	-31	14	58	70
24	-80	37	154	190	-23	16	59	79
25	-107	26	160	186	7	20	51	89
26	-59	39	136	175	-44	10	60	66
27	-39	43	125	168	-74	10	66	49
28	-31	47	125	172	-67	3	64	58
29	22	69	116	185	-63	9	60	47
30	35	81	128	209	-64	19	64	45
31	121	119	116	235	-10	10	42	65
32	-13	70	153	223	0	13	51	89

Segment clusters comprise 1-7, 8-17, 18-28, and 19-32.

Table 2. Measurement Values of 32 Segments in a ‘Circumferential Enlarged Intima’ Section.

Segment	T-FU2	r-lu-VW	VW-dik	r-lumen	T-FU1	intdik	meddik	advdik
1	-608	53	713	766	194	252	173	288
2	-462	114	690	804	116	244	191	254
3	-349	171	690	861	92	230	200	261
4	-370	180	730	910	96	238	211	280
5	-171	270	711	981	67	226	215	270
6	29	363	697	1060	128	223	190	284
7	157	426	696	1123	57	204	213	280
8	95	410	725	1135	235	268	163	294
9	407	523	638	1161	74	225	188	225
10	657	620	583	1203	96	211	162	210
11	701	631	562	1193	55	166	169	227
12	435	515	594	1109	94	160	167	268
13	368	461	554	1015	41	172	171	211
14	58	335	611	946	65	164	182	265
15	114	338	562	899	3	172	186	204
16	-101	249	599	847	45	197	185	217
17	-342	155	652	808	243	300	136	216
18	-491	109	708	817	345	317	121	270
19	-380	156	693	849	299	280	131	281
20	-563	103	769	872	250	297	173	300
21	-529	136	801	937	332	293	156	352
22	-489	172	833	1005	376	272	152	408
23	63	377	691	1068	355	287	112	292
24	452	544	637	1181	298	268	113	256
25	978	750	521	1270	79	194	147	180
26	718	656	594	1250	160	252	145	197
27	433	538	643	1181	316	245	109	289
28	315	463	611	1074	243	237	123	252
29	70	358	646	1004	301	227	115	303
30	-126	258	643	901	219	227	141	274
31	-357	158	673	830	222	235	150	288
32	-554	80	714	794	222	235	164	315

Segment clusters comprise 1-10, 11-14, 15-18, 19-22, 23-25, and 26-32.

Table 3. Measurement Values of 32 Segments in a ‘Unilateral Atherosclerosis’ Section.

Segment	T-FU2	rlu-VW	VWdik	Rlu	T-FU1	INTd	MEDd	ADVd
1	-1528	-469	590	121	483	433	36	121
2	-1608	-498	611	112	519	464	31	116
3	-1741	-543	655	113	576	493	26	136
4	-1823	-569	685	116	545	499	47	140
5	-1671	-509	653	145	477	497	59	98
6	-913	-201	511	311	334	357	59	96
7	-356	28	412	440	219	240	64	107
8	-199	100	399	499	245	207	51	141
9	260	286	312	598	139	118	58	136
10	215	263	311	574	172	92	46	172
11	156	231	306	537	146	83	54	169
12	163	228	292	520	119	61	58	173
13	310	272	234	506	63	55	57	122
14	309	276	244	520	94	48	50	147
15	462	328	194	522	48	44	49	101
16	220	234	247	481	119	73	43	131
17	207	227	247	474	58	76	63	108
18	141	202	263	465	76	81	62	119
19	91	180	270	450	62	75	69	126
20	4	145	286	432	37	77	83	127
21	-1	146	292	438	73	78	73	141
22	112	195	277	472	93	86	61	130
23	183	231	280	511	113	68	56	157
24	192	246	301	547	169	81	44	177
25	59	208	358	566	169	71	63	224
26	-113	126	365	491	119	113	82	170
27	-449	-11	427	415	207	170	73	184
28	-383	-1	381	380	212	189	56	135
29	-578	-87	404	317	234	246	57	102
30	-850	-200	450	249	314	311	45	93
31	-1224	-347	529	182	428	368	34	127
32	-1286	-381	524	143	432	391	31	102

Segment clusters comprise 1-4, 5-8, 9-11, 12-15, 16-21, 22-24, and 25-32.

Table 4. Measurement Values of 32 Segments in a ‘Circumferential Atherosclerosis’ Section.

Segment	T-FU2	rlu-VW	VWdik	Rlu	T-FU1	INTd	MEDd	ADVd
1	-1972	-493	986	493	718	724	89	173
2	-2201	-573	1055	482	639	718	139	198
3	-2315	-609	1097	488	634	707	154	236
4	-2470	-654	1162	507	665	764	166	232
5	-2578	-674	1230	555	763	785	156	289
6	-2612	-668	1275	607	818	780	153	343
7	-2351	-561	1228	666	791	774	146	308
8	-2081	-448	1185	736	744	760	147	278
9	-1796	-325	1146	821	738	721	136	288
10	-238	286	810	1096	376	383	145	283
11	-466	185	837	1022	484	450	118	269
12	-911	2	916	919	542	472	125	319
13	-1585	-283	1020	737	693	600	109	311
14	-1765	-377	1012	635	545	575	156	281
15	-2143	-543	1057	514	654	657	134	266
16	-2293	-614	1065	450	503	665	187	213
17	-2464	-682	1101	420	645	739	152	210
18	-2713	-774	1164	390	732	796	144	224
19	-3056	-893	1271	378	908	836	121	314
20	-3553	-1057	1438	381	941	882	166	390
21	-3661	-1086	1489	404	1044	907	148	434
22	-3704	-1080	1544	464	1092	923	151	470
23	-3310	-926	1459	533	1065	861	131	467
24	-2149	-480	1189	709	865	702	108	378
25	-1936	-393	1151	758	916	742	78	330
26	-1108	-65	978	913	771	591	69	318
27	-1008	-38	931	893	713	573	73	285
28	-1517	-269	978	708	837	667	47	264
29	-1450	-257	935	678	734	604	67	264
30	-1539	-304	930	626	733	629	66	235
31	-1694	-374	946	571	677	657	90	199
32	-1935	-467	1002	535	723	708	93	201

Segment clusters comprise 1-6, 7-9, 10-19, 20-27, and 28-32.

Triplets

Each section consisted of 16 triplets, and each triplet consisted of 20 associated data points.

After data conversion to linear courses (Δ), various triplets showed that Δ T-FU2 and Δ Rlu-

VWd (R^2 always > 0.95) alternated from increasing to decreasing order. Regardless of a section's histological rating, nine triplets showed a decrease and seven triplets an increase. Increasing and decreasing triplets were not always successive.

The paths followed by ΔRlu -VWd, ΔVWd , ΔRlu , $\Delta INTd$, $\Delta MEDd$, and $\Delta ADVd$ within each triplet were unique and differed in various triplets. Marks were discerned within several triplets (asynchronous, course-dependent, section-independent): ΔRlu -VWd ≈ 0 resulted in $\Delta VWd \approx \Delta Rlu$, $\Delta VWd \approx 0$ gives ΔRlu -VWd $\approx \Delta Rlu$, and $\Delta Rlu \approx 0$ resulted in $\Delta VWd \approx -\Delta Rlu$ -VWd. Asynchronous $\Delta INTd$, $\Delta MEDd$, or $\Delta ADVd \approx 0$ was also encountered without noticeable influence on the ΔVWd sequence. Even two of these being ≈ 0 did not influence the ΔVWd course. Marks in various triplets were not accompanied by ΔT -FU2 or ΔRlu -VWd similarity.

Triplet interaction

The ΔVWd , ΔRlu , $\Delta INTd$, $\Delta MEDd$, and $\Delta ADVd$ values of all triplets originating from each section were set against ΔRlu -VWd separately, resulting in summed trendline a-values for ΔVWd and $\Delta Rlu = 1$ (Table 5). Consecutive triplets did not constitute a systemic sequence, but ordering in descending order based on ΔVWd trendline a-values obtained a regular sequence. Three stages were observed: stage 1 marked by trendline a-values ΔVWd and $\Delta Rlu > 0$; stage 2 marked by antagonistic a-values ΔVWd and ΔRlu ; stage 3 marked by a-values ΔVWd and $\Delta Rlu < 0$. Transition stage 1 to stage 2 was marked by a-value $\Delta VWd = 0$ and by a-value $\Delta Rlu = 1$, whereas transition from stage 2 to stage 3 presented the opposite (i.e., a-value $\Delta VWd = 1$ and a-value $\Delta Rlu = 0$). All sections showed three stages except 'extreme unilateral atherosclerosis', which lacked stage 1 due to a ΔVWd trendline a-value shift from stage 1 to stage 3.

202

203 **Table 5. Scatter Diagram Results.**

Normal		$\Delta V W d$	$\Delta R l u$	$\Delta I N T d$	$\Delta M E D d$	$\Delta A D V d$
stage 1	(11-13)	$y = 7.6157x - 26.171$	$y = 8.6159x - 26.171$	$y = -3.6986x + 12.18$	$y = 8.9594x - 31.075$	$y = 2.3548x - 7.2757$
	(3-5)	$y = 0.9273x + 3.009$	$y = 1.9273x + 3.0086$	$y = -0.2813x - 0.5078$	$y = 1.1283x + 1.5693$	$y = 0.0803x + 1.9477$
stage 2	(19-21)	$y = -0.1983x + 0.3041$	$y = 0.8017x + 0.3037$	$y = -0.0281x - 0.4178$	$y = -0.3569x + 0.094$	$y = 0.1867x + 0.6283$
	(23-25)	$y = -0.2155x + 0.3957$	$y = 0.7845x + 0.3942$	$y = 0.1094x + 0.5529$	$y = -0.3642x - 1.1637$	$y = 0.0393x + 1.0061$
	(13-15)	$y = -0.2152x - 0.1536$	$y = 0.7849x - 0.1533$	$y = 0.2189x - 0.0907$	$y = -0.4797x + 0.7966$	$y = 0.0456x - 0.8595$
	(9-11)	$y = -0.263x + 0.6603$	$y = 0.737x + 0.6615$	$y = -0.583x + 0.3723$	$y = -1.1775x + 1.7978$	$y = 1.4974x - 1.509$
	(27-29)	$y = -0.4643x + 0.1325$	$y = 0.5357x + 0.1325$	$y = 0.7248x - 0.9672$	$y = -0.1049x - 0.2067$	$y = -1.0842x + 1.3059$
	(21-23)	$y = -0.5926x - 0.6261$	$y = 0.4074x - 0.6292$	$y = -0.5616x - 0.711$	$y = 0.0781x - 0.3047$	$y = -0.1092x + 0.3874$
	(17-19)	$y = -0.5944x - 0.2178$	$y = 0.4056x - 0.2178$	$y = 0.086x + 0.198$	$y = -0.4227x - 0.1787$	$y = -0.2578x - 0.234$
	(7-9)	$y = -0.6364x + 0.1033$	$y = 0.3636x + 0.1027$	$y = 0.0146x + 0.301$	$y = -0.1011x - 0.0792$	$y = -0.5498x - 0.1188$
	(1-3)	$y = -0.6428x - 0.424$	$y = 0.3572x - 0.4247$	$y = -0.3765x - 0.6698$	$y = 0.6775x + 2.5999$	$y = -0.9437x - 2.3548$
	(31-1)	$y = -0.7474x - 0.0235$	$y = 0.2526x - 0.0235$	$y = -0.0501x + 0.0185$	$y = -0.1982x - 0.0682$	$y = -0.499x + 0.0259$
	(29-31)	$y = -0.9225x + 2.3182$	$y = 0.0775x + 2.319$	$y = -0.7419x + 1.871$	$y = -1.0645x + 1.7754$	$y = 0.884x - 1.3226$
stage 3	(5-7)	$y = -1.3865x - 0.9985$	$y = -0.3864x - 0.9985$	$y = 0.3197x + 0.1872$	$y = -0.4367x - 0.2977$	$y = -1.2694x - 0.8887$
	(25-27)	$y = -1.6533x - 0.3501$	$y = -0.6532x - 0.3507$	$y = -1.3156x + 0.5848$	$y = 0.3858x + 0.4492$	$y = -0.7234x - 1.3847$
	(15-17)	$y = -4.2335x - 0.7513$	$y = -3.2336x - 0.751$	$y = -2.2931x - 0.5155$	$y = -0.948x - 0.1974$	$y = -0.9925x - 0.0375$
Circumferential enlarged intima		$\Delta V W d$	$\Delta R l u$	$\Delta I N T d$	$\Delta M E D d$	$\Delta A D V d$
stage 1	(25-27)	$y = 0.9555x + 16.208$	$y = 1.9555x + 16.207$	$y = 2.6479x + 30.55$	$y = 1.3403x + 12.251$	$y = -3.0328x - 26.592$
stage 2	(9-11)	$y = -0.393x - 1.6902$	$y = 0.607x - 1.6902$	$y = 0.3482x - 4.828$	$y = -0.3746x + 1.0657$	$y = -0.3666x + 2.0711$
	(5-7)	$y = -0.4888x + 3.075$	$y = 0.5112x + 3.075$	$y = 0.5739x - 5.6071$	$y = -1.6454x + 12.777$	$y = 0.5827x - 4.0956$
	(19-21)	$y = -0.5123x + 4.8784$	$y = 0.4877x + 4.8834$	$y = -0.2322x + 0.3748$	$y = -0.6747x + 0.555$	$y = 0.3947x + 3.9515$

	(31-1)	$y = -0.5272x + 0.0489$	$y = 0.4728x + 0.049$	$y = -0.0193x - 0.0508$	$y = -0.1788x - 0.0139$	$y = -0.3291x + 0.1137$
	(3-5)	$y = -0.7208x + 4.6225$	$y = 0.2792x + 4.6225$	$y = -0.2568x + 1.074$	$y = -0.0987x + 1.2549$	$y = -0.3654x + 2.2936$
	(17-19)	$y = -0.7492x + 2.0625$	$y = 0.2508x + 2.0715$	$y = -0.5627x - 0.9536$	$y = 0.2711x - 0.2666$	$y = -0.4576x + 3.2857$
	(13-15)	$y = -0.8344x - 4.7317$	$y = 0.1656x - 4.7407$	$y = 0.1177x + 0.7193$	$y = -0.0522x + 0.4348$	$y = -0.8999x - 5.8899$
	(7-9)	$y = -0.8979x + 1.4034$	$y = 0.1021x + 1.4044$	$y = -0.8301x + 5.053$	$y = 0.577x - 4.0115$	$y = -0.6448x + 0.3619$
	(21-23)	$y = -1.0217x + 6.8259$	$y = -0.0217x + 6.8289$	$y = 0.21x - 2.7985$	$y = -0.2137x + 0.3656$	$y = -1.0181x + 9.2658$
stage 3	(11-13)	$y = -1.169x - 10.359$	$y = -0.169x - 10.359$	$y = 0.28x + 2.6695$	$y = 0.1035x + 1.0029$	$y = -1.5525x - 14.03$
	(23-25)	$y = -1.6237x + 21.723$	$y = -0.6237x + 21.718$	$y = -1.413x + 21.636$	$y = 0.8776x - 14.578$	$y = -1.0883x + 14.655$
	(27-29)	$y = -2.1822x - 19.542$	$y = -1.1822x - 19.538$	$y = 0.0383x - 0.5499$	$y = 0.7076x + 6.6792$	$y = -2.9282x - 25.667$
	(15-17)	$y = -3.8237x - 30.381$	$y = -2.8237x - 30.382$	$y = -17.847x - 156.59$	$y = 10.882x + 96.895$	$y = 3.1415x + 29.313$
	(1-3)	$y = -5.1462x + 29.249$	$y = -4.1462x + 29.249$	$y = 1.3347x - 8.9773$	$y = 2.1271x - 11.242$	$y = -8.6081x + 49.468$
	(29-31)	$y = -39.482x - 393.85$	$y = -38.482x - 393.84$	$y = -9.1928x - 91.658$	$y = 20.771x + 209.67$	$y = -51.06x - 511.86$
Unilateral atherosclerosis						
		ΔVVd	ΔRIu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 1	(31-1)	$y = 0.0787x - 0.234$	$y = 1.0787x - 0.234$	$y = -0.6733x + 0.0551$	$y = 0.0817x - 0.0392$	$y = 0.6705x - 0.2503$
	(9-11)	$y = 0.3337x + 0.6282$	$y = 1.3337x + 0.6282$	$y = -1.9837x - 7.2209$	$y = -2.2147x - 6.3297$	$y = 4.5321x + 14.179$
stage 2	(19-21)	$y = -0.309x + 0.5903$	$y = 0.691x + 0.5903$	$y = -0.0112x + 0.1585$	$y = -0.6775x - 0.9849$	$y = 0.3798x + 1.4167$
	(5-7)	$y = -0.5371x + 2.3427$	$y = 0.4629x + 2.3427$	$y = -0.3009x - 4.7293$	$y = -0.0668x + 2.0772$	$y = -0.1694x + 4.9938$
	(15-17)	$y = -0.622x - 0.4721$	$y = 0.378x - 0.4751$	$y = -0.309x + 0.0246$	$y = 0.2988x + 2.223$	$y = -0.6118x - 2.7196$
	(7-9)	$y = -0.6473x + 3.3671$	$y = 0.3527x + 3.3671$	$y = -0.4874x + 0.1764$	$y = 0.173x - 2.5653$	$y = -0.3329x + 5.756$
	(23-25)	$y = -0.6699x + 3.1096$	$y = 0.3301x + 3.1056$	$y = 0.4221x + 0.6445$	$y = -0.576x - 0.3093$	$y = -0.516x + 2.7755$
	(3-5)	$y = -0.714x + 1.1085$	$y = 0.286x + 1.1085$	$y = -0.0845x + 0.2963$	$y = -0.0997x + 1.7926$	$y = -0.5297x - 0.9799$
	(27-29)	$y = -0.72x - 3.8693$	$y = 0.28x - 3.8683$	$y = -0.3872x + 2.3138$	$y = -0.1797x - 1.5122$	$y = -0.153x - 4.6748$
	(11-13)	$y = -0.9392x - 1.7053$	$y = 0.0608x - 1.7058$	$y = 0.3265x - 2.07$	$y = -0.1104x + 0.4035$	$y = -1.1553x - 0.0397$
	(25-27)	$y = -0.9807x - 7.3002$	$y = 0.0193x - 7.3047$	$y = -0.2681x + 2.0146$	$y = 0.5001x + 5.998$	$y = -1.2127x - 15.314$
stage 3	(29-31)	$y = -1.003x - 6.7814$	$y = -0.003x - 6.7814$	$y = 0.2713x + 9.6603$	$y = 0.0121x - 0.9819$	$y = -1.2863x - 15.455$
	(13-15)	$y = -1.2941x + 1.6153$	$y = -0.2941x + 1.6153$	$y = 0.0891x - 0.8099$	$y = 0.1238x - 0.7668$	$y = -1.507x + 3.1919$
	(21-23)	$y = -1.4816x + 5.7353$	$y = -0.4816x + 5.7358$	$y = 2.1461x - 9.7238$	$y = -0.4841x + 1.2081$	$y = -3.1436x + 14.251$
	(1-3)	$y = -1.604x - 2.6381$	$y = -0.604x - 2.6381$	$y = 0.0682x + 3.251$	$y = -0.0429x - 0.6246$	$y = -1.6292x - 5.2644$

(17-19)		$y = -2.8389x - 5.4709$	$y = -1.8389x - 5.4709$	$y = -3.7386x - 8.7361$	$y = 2.3556x + 5.784$	$y = -1.4559x - 2.5183$
Circumferential atherosclerosis						
		ΔVVd	ΔRIu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 1	(15-17)	$y = 7.3116x + 52.816$	$y = 8.3116x + 52.816$	$y = 16.917x + 121.22$	$y = -22.078x - 151.94$	$y = 12.472x + 83.535$
	(7-9)	$y = 0.4105x - 8.9468$	$y = 1.4105x - 8.9468$	$y = -2.3582x + 25.243$	$y = -1.1423x + 13.02$	$y = 3.9109x - 47.209$
	(3-5)	$y = 0.1175x + 7.0294$	$y = 1.1175x + 7.0294$	$y = -1.4501x - 0.8144$	$y = -0.8451x - 2.6804$	$y = 2.4127x + 10.524$
stage 2	(11-13)	$y = -0.231x + 3.7454$	$y = 0.769x + 3.7444$	$y = -1.03x - 16.602$	$y = 0.2261x + 4.864$	$y = 0.5728x + 15.487$
	(27-29)	$y = -0.3663x - 3.8027$	$y = 0.6336x - 3.8311$	$y = -0.6447x - 5.5001$	$y = 0.1906x + 1.7906$	$y = 0.0878x - 0.1002$
	(25-27)	$y = -0.421x - 3.5213$	$y = 0.579x - 3.5213$	$y = -0.4459x - 0.5729$	$y = -0.0456x + 0.5292$	$y = 0.0705x - 3.4786$
	(9-11)	$y = -0.5086x - 2.4846$	$y = 0.4914x - 2.4746$	$y = -0.5706x + 0.9763$	$y = 0.0501x - 2.2035$	$y = 0.0119x - 1.2544$
	(31-1)	$y = -0.5935x + 0.1002$	$y = 0.4065x + 0.0999$	$y = -0.5473x - 0.0048$	$y = -0.0343x + 0.0145$	$y = -0.0343x + 0.0145$
	(1-3)	$y = -0.6217x + 1.9193$	$y = 0.3783x + 1.9203$	$y = -0.115x - 1.5121$	$y = -0.7722x - 1.2299$	$y = 0.2655x + 4.6623$
	(23-25)	$y = -0.6492x + 1.9002$	$y = 0.3508x + 1.9002$	$y = -0.5531x + 8.8274$	$y = 0.0167x - 3.0843$	$y = -0.1128x - 3.8509$
	(13-15)	$y = -0.7407x - 7.7683$	$y = 0.2593x - 7.7683$	$y = -1.4841x - 16.453$	$y = 0.9345x + 13.44$	$y = -0.1911x - 4.7538$
	(19-21)	$y = -0.8529x + 2.7078$	$y = 0.1471x + 2.7038$	$y = -0.1555x + 2.0917$	$y = -0.4562x - 3.0373$	$y = -0.2412x + 3.6494$
	(29-31)	$y = -0.8567x - 4.4847$	$y = 0.1433x - 4.4852$	$y = -0.102x + 2.0679$	$y = -1.0908x - 5.2542$	$y = 0.3362x - 1.2989$
	(5-7)	$y = -0.9203x + 5.0949$	$y = 0.0797x + 5.0949$	$y = -0.0077x - 0.5026$	$y = -0.0369x - 0.2901$	$y = -0.8757x + 5.8877$
	(21-23)	$y = -0.9466x + 6.0568$	$y = 0.0534x + 6.0548$	$y = -0.527x + 1.875$	$y = -0.1509x + 0.3522$	$y = -0.2687x + 3.8266$
stage 3	(17-19)	$y = -1.7118x - 9.6206$	$y = -0.7118x - 9.6206$	$y = 0.6809x + 12$	$y = 0.581x + 4.5885$	$y = 0.581x + 4.5885$
Extreme unilateral atherosclerosis						
		ΔVVd	ΔRIu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 2	(5-7)	$y = -0.2939x + 4.9353$	$y = 0.7061x + 4.9353$	$y = -0.3342x + 2.9221$	$y = -0.1302x + 0.3114$	$y = 0.1706x + 1.7009$
	(9-11)	$y = -0.3091x - 0.6248$	$y = 0.6909x - 0.6248$	$y = -0.9362x - 18.244$	$y = 0.1113x + 4.4967$	$y = 0.5157x + 13.121$
	(1-3)	$y = -0.4058x + 2.0641$	$y = 0.5942x + 2.0641$	$y = -0.7378x - 0.6671$	$y = 0.0959x - 0.4716$	$y = 0.2361x + 3.2028$
	(7-9)	$y = -0.5283x - 1.1638$	$y = 0.4717x - 1.1638$	$y = -0.4966x - 0.5045$	$y = -0.0094x - 0.1072$	$y = -0.0223x - 0.555$
	(15-17)	$y = -0.6198x - 2.9083$	$y = 0.3802x - 2.9083$	$y = -0.735x - 9.6632$	$y = 0.3992x + 7.4305$	$y = -0.2841x - 0.6776$
	(11-13)	$y = -0.6462x + 1.8993$	$y = 0.3538x + 1.8993$	$y = -1.8108x - 0.972$	$y = 1.1589x + 3.6811$	$y = 0.0057x - 0.8048$
	(19-21)	$y = -0.7316x - 2.4254$	$y = 0.2684x - 2.4254$	$y = 38.703x + 735.98$	$y = -17.382x - 324.65$	$y = -22.051x - 413.7$
	(3-5)	$y = -0.7372x + 9.0328$	$y = 0.2628x + 9.0328$	$y = -0.7389x + 6.6779$	$y = 0.023x + 0.4632$	$y = -0.0213x + 0.9907$

	(31-1)	$y = -0.8262x + 0.0652$	$y = 0.1738x + 0.0645$	$y = 0.1028x + 0.0109$	$y = -0.4553x - 0.0136$	$y = -0.4737x + 0.0678$
	(29-31)	$y = -0.8395x - 0.229$	$y = 0.1605x - 0.229$	$y = -1.3479x + 8.1418$	$y = 0.3232x - 3.0899$	$y = 0.1852x - 5.2778$
stage 3	(23-25)	$y = -1.3628x - 6.5266$	$y = -0.3628x - 6.5266$	$y = -3.8562x - 25.599$	$y = 2.1118x + 18.85$	$y = 0.3816x + 0.2274$
	(27-29)	$y = -1.3843x + 4.4681$	$y = -0.3843x + 4.4681$	$y = -0.0526x - 15.13$	$y = 0.2781x - 0.3223$	$y = -1.6099x + 19.921$
	(13-15)	$y = -1.8098x - 5.6616$	$y = -0.8098x - 5.6616$	$y = -0.0513x + 7.0871$	$y = 0.0246x - 5.7205$	$y = -1.7831x - 7.0192$
	(21-23)	$y = -1.9352x - 10.524$	$y = -0.9352x - 10.524$	$y = -0.6001x + 0.9081$	$y = -1.9618x - 19.55$	$y = 0.6267x + 8.1093$
	(25-27)	$y = -2.1057x - 9.653$	$y = -1.1057x - 9.653$	$y = 1.3281x + 13.742$	$y = 0.2048x + 1.3559$	$y = -3.6386x - 24.749$
	(17-19)	$y = -7.6744x - 201.48$	$y = -6.6744x - 201.48$	$y = -18.023x - 503.12$	$y = 8.7022x + 247.94$	$y = 1.6466x + 53.698$

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205 $\Delta Rlu-VWd$ was used as the reference. Triplets are arranged in descending order based on $\Delta Rlu-VWd$ trendline a-values. Bold marks the transition point from

206 stage 2 to stage 3 by ΔRlu a-value ≈ 0 and ΔVWd a-value ≈ 1 .

The strictly ordered course of $\Delta V W d$ and $\Delta R l u$ was not followed by a similar $\Delta I N T d$, $\Delta M E D d$, and $\Delta A D V d$ pattern; their singular courses always changed from one triplet to the next. This sometimes resulted in a parallel course with either $\Delta V W d$ or $\Delta R l u$ based on a-value similarity. Due to their asynchronous course, trendline a-value ≈ 0 was reached in different triplets.

The same $\Delta V W d$ trendline a-value in different sections regardless of pathology was accompanied by similar $\Delta R l u$ a-values but different b-values (i.e., the same direction (trendline slope) but on a different level).

Triplet course expressed by semi-ranges

The paths followed in all sections and triplets expressed by semi-ranges (last value in triplet series minus first value) are presented in Table 6. The systems order encountered in Table 5 was no longer recognizable. Stages 1, 2, and 3 were still discerned: stage 1 defined by $\Delta V W d$ and $\Delta R l u$ semi-ranges > 0 , stage 2 by antagonistic semi-ranges, and both < 0 in stage 3. Transition from stage 1 to stage 2 was not defined by semi-ranges; all values differed in various sections. The changeover from stage 2 to stage 3 was recognizable by semi-range value $\Delta R l u \approx 0$, accompanied by similar semi-ranges for $\Delta R l u - V W d$ and $\Delta V W d$ but antagonistic in sign. This feature was found in all sections though semi-range values differed greatly.

226 **Table 6. Semi-ranges Comprising the Last Value in a Triplet Series Minus the First Value.**

Normal		$\Delta T\text{-fu1}$	$\Delta T\text{-FU2}$	$\Delta Rlu\text{-VWd}$	ΔVWd	ΔRlu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 1	(11-13)	-9.5	-2.8	0.5	3.8	4.3	-1.8	4.4	1.2
	(3-5)	-9.2	4.0	3.7	3.5	7.2	-1.1	4.2	0.3
stage 2	(19-21)	-7.5	-18.8	-8.6	1.7	-6.9	0.2	3.1	-1.6
	(23-25)	4.2	10.6	4.8	-1.0	3.7	0.5	-1.7	0.2
	(13-15)	1.3	2.4	1.1	-0.2	0.8	0.2	-0.5	0.0
	(9-11)	-9.0	-6.3	-2.8	0.7	-2.0	1.6	3.3	-4.1
	(27-29)	-0.5	8.4	3.4	-1.6	1.8	2.5	-0.4	-3.7
	(21-23)	-7.6	23.7	9.1	-5.4	3.7	-5.1	0.7	-1.0
	(17-19)	-6.1	-23.4	-9.0	5.4	-3.7	-0.8	3.8	2.3
	(7-9)	2.7	-21.7	-8.2	5.2	-3.0	-0.1	0.8	4.5
	(1-3)	-35.7	35.2	13.3	-8.6	4.8	-5.0	9.0	-12.6
	(31-1)	0.1	-1.6	-0.6	0.4	-0.1	0.0	0.1	0.3
	(29-31)	10.6	13.7	4.7	-4.3	0.4	-3.5	-5.0	4.1
	(5-7)	0.3	-12.6	-3.7	5.2	1.4	-1.2	1.6	4.7
stage 3	(25-27)	4.1	-5.4	-1.5	2.4	1.0	1.9	-0.6	1.1
	(15-17)	1.5	-6.9	-1.1	4.7	3.6	2.5	1.0	1.1
sum		-60.1	-1.4	5.2	11.8	17.0	-9.0	24.0	-3.2
Circumferential enlarged intima									
		$\Delta T\text{-fu1}$	$\Delta T\text{-FU2}$	$\Delta Rlu\text{-VWd}$	ΔVWd	ΔRlu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 1	(25-27)	14.4	-4.9	-4.7	-4.5	-9.2	-12.4	-6.3	14.2
stage 2	(9-11)	-11.9	-39.1	-16.3	6.4	-9.9	-5.7	6.1	6.0
	(5-7)	-24.9	-13.9	-5.6	2.7	-2.9	-3.2	9.2	-3.3
	(19-21)	24.8	41.3	16.4	-8.4	8.0	-3.8	-11.1	6.5
	(31-1)	0.0	-2.5	-1.0	0.5	-0.5	0.0	0.2	0.3
	(3-5)	-6.5	41.9	15.4	-11.1	4.3	-4.0	-1.5	-5.6
	(17-19)	-28.0	49.3	17.9	-13.4	4.5	-10.1	4.9	-8.2
	(13-15)	-16.6	69.4	24.5	-20.4	4.1	2.9	-1.3	-22.0
	(7-9)	-64.4	70.9	24.5	-22.0	2.5	-20.3	14.1	-15.8
	(21-23)	-12.3	97.3	32.2	-32.9	-0.7	6.8	-6.9	-32.8
stage 3	(11-13)	-17.7	37.9	12.0	-14.0	-2.0	3.3	1.2	-18.6
	(23-25)	-30.9	26.3	7.3	-11.8	-4.5	-10.2	6.4	-7.9
	(27-29)	25.0	-24.2	-5.8	12.7	6.9	-0.2	-4.1	17.0
	(15-17)	29.9	-4.8	-0.8	3.1	2.3	14.6	-8.9	-2.6
	(1-3)	10.3	-6.4	-0.9	4.6	3.7	-1.2	-1.9	7.7
	(29-31)	16.1	-6.5	-0.2	6.2	6.1	1.4	-3.3	8.1
sum		-92.8	331.9	114.8	102.2	12.6	-42.1	-3.1	-56.9
Unilateral atherosclerosis									
		$\Delta T\text{-fu1}$	$\Delta T\text{-FU2}$	$\Delta Rlu\text{-VWd}$	ΔVWd	ΔRlu	$\Delta INTd$	$\Delta MEDd$	$\Delta ADVd$
stage 1	(31-1)	0.1	-0.9	-0.5	0.0	-0.5	0.3	0.0	-0.3

	(9-11)	-11.4	-2.7	-1.6	-0.5	-2.2	3.2	3.6	-7.4
stage 2	(19-21)	11.7	15.6	6.8	-2.1	4.7	-0.1	-4.6	2.6
	(5-7)	5.1	-38.2	-15.1	8.1	-7.0	4.5	1.0	2.6
	(15-17)	-25.1	43.4	16.5	-10.3	6.3	-5.1	4.9	-10.1
	(7-9)	-25.3	57.4	21.7	-14.0	7.6	-10.6	3.7	-7.2
	(23-25)	-10.7	-27.0	-10.1	6.8	-3.3	-4.3	5.8	5.2
	(3-5)	-6.8	44.5	16.4	-11.7	4.7	-1.4	-1.6	-8.7
	(27-29)	3.3	-49.6	-18.2	13.1	-5.1	7.1	3.3	2.8
	(11-13)	-5.5	26.7	9.1	-8.5	0.6	3.0	-1.0	-10.5
	(25-27)	26.1	-31.4	-10.5	10.3	-0.2	2.8	-5.3	12.8
stage 3	(29-31)	6.7	-19.3	-6.4	6.4	0.0	-1.7	-0.1	8.3
	(13-15)	-14.8	29.2	8.9	-11.5	-2.6	0.8	1.1	-13.4
	(21-23)	0.1	-7.9	-2.3	3.4	1.1	-4.9	1.1	7.2
	(1-3)	4.1	-10.0	-2.8	4.5	1.7	-0.2	0.1	4.5
	(17-19)	-6.2	3.0	0.6	-1.8	-1.1	-2.3	1.5	-0.9
	sum	-48.7	32.6	12.4	-7.9	4.5	-8.8	13.6	-12.6

Circumferential atherosclerosis

		Δ FU1	Δ T-FU2	Δ Rlu-VWd	Δ VWd	Δ Rlu	Δ INTd	Δ MEDd	Δ ADVd
stage 1	(15-17)	55.6	-4.0	0.8	5.5	6.3	12.8	-16.7	9.4
	(7-9)	7.5	3.1	2.0	0.8	2.8	-4.6	-2.2	7.7
	(3-5)	12.8	9.1	4.8	0.6	5.4	-7.0	-4.1	11.7
stage 2	(11-13)	17.7	-43.3	-19.4	4.5	-14.9	20.0	-4.4	-11.1
	(27-29)	-43.3	109.3	46.2	-16.9	29.3	-29.8	8.8	4.1
	(25-27)	16.2	-138.4	-57.2	24.1	-33.1	25.5	2.6	-4.0
	(9-11)	89.1	-339.3	-135.3	68.8	-66.5	77.2	-6.8	-1.6
	(31-1)	0.6	-3.1	-1.2	0.7	-0.5	0.6	0.0	0.0
	(1-3)	14.3	22.0	8.4	-5.2	3.2	-1.0	-6.5	2.2
	(23-25)	47.6	-180.3	-68.1	44.2	-23.9	37.7	-1.1	7.7
	(13-15)	48.7	-37.7	-13.8	10.2	-3.6	20.4	-12.9	2.6
	(19-21)	13.3	73.7	25.8	-22.0	3.8	-4.0	-11.8	-6.2
	(29-31)	-10.7	-12.6	-4.4	3.8	-0.6	0.5	4.8	-1.5
	(5-7)	-15.6	56.3	19.3	-17.7	1.5	-0.1	-0.7	-16.9
	(21-23)	-13.9	83.1	28.2	-26.7	1.5	-14.9	-4.3	-7.6
stage 3	(17-19)	16.8	-18.0	-4.9	8.3	3.5	-3.3	-2.8	14.4
	sum	256.7	-420.1	-168.7	82.8	-85.8	129.9	-58.0	10.9

Extreme unilateral atherosclerosis

		Δ T-fu1	Δ T-FU2	Δ Rlu-VWd	Δ VWd	Δ Rlu	Δ INTd	Δ MEDd	Δ ADVd
	(5-7)	3.6	85.4	37.2	-10.9	26.3	-12.4	-4.8	6.4
	(9-11)	-26.4	94.8	41.1	-12.7	28.4	-38.4	4.6	21.2
	(1-3)	-7.2	29.6	12.3	-5.0	7.3	-9.1	1.2	2.9
	(7-9)	108.2	-547.2	-216.4	114.3	-102.1	107.5	2.0	4.8
	(15-17)	65.2	-94.0	-35.9	22.2	-13.6	26.4	-14.3	10.2
	(11-13)	93.2	-59.8	-22.6	14.6	-8.0	40.9	-26.2	-0.1
	(19-21)	49.0	2.6	1.0	-0.7	0.3	36.9	-16.6	-21.0
	(3-5)	28.8	-97.9	-35.8	26.4	-9.4	26.4	-0.8	0.8

(31-1)	0.7	3.8	1.3	-1.1	0.2	0.1	-0.6	-0.6
(29-31)	16.5	-25.9	-9.1	7.7	-1.5	12.3	-3.0	-1.7
(23-25)	-30.4	13.3	3.9	-5.4	-1.4	-15.2	8.3	1.5
(27-29)	29.0	-44.3	-13.1	18.1	5.0	0.7	-3.6	21.1
(13-15)	-28.7	58.0	15.2	-27.6	-12.3	-0.8	0.4	-27.2
(21-23)	38.5	-39.7	-10.1	19.5	9.4	6.0	-6.3	19.8
(25-27)	10.3	-15.5	-3.8	8.0	4.2	-5.0	-0.8	13.8
(17-19)	39.4	-11.3	-1.2	9.0	7.8	21.0	-10.2	-1.9
sum	389.80	-648.08	-235.9	176.4	-59.5	197.31	-70.7	49.8

Triplets are arranged in descending order based on ΔRlu -VWd trendline a-values. Bold marks the transition point from stage 2 to stage 3.

The $\Delta INTd$, $\Delta MEDd$, and $\Delta ADVd$ semi-ranges mutually changed from one triplet to the next, increase or decrease of one opposed to the decrease or increase of the other two, a counter-balancing system found in all sections regardless of histological rating. The summed values presented their mutual distribution: ‘normal’, semi-range $\Delta MEDd$ opposed by semi-ranges $\Delta INTd$ and $\Delta ADVd$; ‘circumferential enlarged intima’, all three had the same sign; ‘unilateral atherosclerosis’, semi-range $\Delta MEDd$ opposed by semi-ranges $\Delta INTd$ and $\Delta ADVd$; and ‘circumferential atherosclerosis’, semi-ranges $\Delta INTd$ and $\Delta ADVd$ opposed by $\Delta MEDd$ (the same in ‘extreme unilateral atherosclerosis’). The last two sections had the largest semi-range $\Delta INTd$ increase together with semi-range $\Delta ADVd$ growth opposed by semi-range $\Delta MEDd$.

Influence of ΔVW composition on ΔRlu

The individual relationship between $\Delta INTd$, $\Delta MEDd$, and $\Delta ADVd$ and ΔRlu was not elucidated. Stage 2 differed strongly from stage 1 and stage 3, most obviously by summed values ΔVWd in ‘normal’, ‘circumferential enlarged intima’, and ‘unilateral atherosclerosis’ sections being predominantly negative due to $-\Delta INT$, $-\Delta ADVd$, and $+\Delta MEDd$. In contrast, ‘circumferential atherosclerosis’ sections presented predominantly positive ΔVWd values due

245 to $+\Delta\text{INTd}$, $-\Delta\text{MEDd}$, and $-\Delta\text{ADVd}$, whereas ‘extreme unilateral atherosclerosis’ had positive
246 ΔVWd values due to $+\Delta\text{INTd}$, $-\Delta\text{MEDd}$, and $+\Delta\text{ADVd}$.

247 Comparisons of semi-range ratios ΔINT , ΔMEDd , or ΔADVd to ΔVWd and ΔRlu showed
248 variability in the single semi-range values (Table 7). Naturally, the summed semi-range
249 values ΔINTd , ΔMEDd , and ΔADVd in proportion to semi-range ΔVWd equaled 1, but in
250 proportion to semi-range ΔRlu a systemic course developed similar to the semi-range ratio of
251 ΔVWd to ΔRlu . These results were found in all sections independent of semi-range ΔINTd ,
252 ΔMEDd , or ΔADVd values.

253 **Table 7. Semi-ranges Δ INTd, Δ MEDd, and Δ ADVd Expressed in Proportion to Δ VWd and Δ Rlu.**

Normal

		Δ INTd/ Δ MEDd/ Δ ADVd ratio Δ VWd				Δ INTd/ Δ MEDd/ Δ ADVd ratio Δ Rlu				Δ VWd/ Δ Rlu
		Δ INTd	Δ MEDd	Δ ADVd	sum	Δ INTd	Δ MEDd	Δ ADVd	sum	
stage 1	(11-13)	-0.5	1.2	0.3	1.0	-0.4	1.0	0.3	0.88	0.88
	(3-5)	-0.3	1.2	0.1	1.0	-0.1	0.6	0.0	0.48	0.48
stage 2	(19-21)	0.1	1.8	-0.9	1.0	0.0	-0.4	0.2	-0.25	-0.25
	(23-25)	-0.5	1.7	-0.2	1.0	0.1	-0.5	0.1	-0.27	-0.27
	(13-15)	-1.0	2.2	-0.2	1.0	0.3	-0.6	0.1	-0.27	-0.27
	(9-11)	2.2	4.5	-5.7	1.0	-0.8	-1.6	2.0	-0.36	-0.36
	(27-29)	-1.6	0.2	2.3	1.0	1.4	-0.2	-2.0	-0.87	-0.87
	(21-23)	0.9	-0.1	0.2	1.0	-1.4	0.2	-0.3	-1.45	-1.45
	(17-19)	-0.1	0.7	0.4	1.0	0.2	-1.0	-0.6	-1.47	-1.47
	(7-9)	0.0	0.2	0.9	1.0	0.0	-0.3	-1.5	-1.75	-1.75
	(1-3)	0.6	-1.1	1.5	1.0	-1.1	1.9	-2.6	-1.80	-1.80
	(31-1)	0.1	0.3	0.7	1.0	-0.2	-0.8	-2.0	-2.96	-2.96
	(29-31)	0.8	1.2	-1.0	1.0	-9.6	-13.7	11.4	-11.90	-11.90
stage 3	(5-7)	-0.2	0.3	0.9	1.0	-0.8	1.1	3.3	3.59	3.59
	(25-27)	0.8	-0.2	0.4	1.0	2.0	-0.6	1.1	2.53	2.53
	(15-17)	0.5	0.2	0.2	1.0	0.7	0.3	0.3	1.31	1.31

Circumferential enlarged intima

		Δ INTd/ Δ MEDd/ Δ ADVd ratio Δ VWd				Δ INTd/ Δ MEDd/ Δ ADVd ratio Δ Rlu				Δ VWd/ Δ Rlu
		Δ INTd	Δ MEDd	Δ ADVd	sum	Δ INTd	Δ MEDd	Δ ADVd	sum	
stage 1	(25-27)	2.8	1.4	-3.2	1.0	1.4	0.7	-1.6	0.5	0.5
stage 2	(9-11)	-0.9	1.0	0.9	1.0	0.6	-0.6	-0.6	-0.6	-0.6
	(5-7)	-1.2	3.4	-1.2	1.0	1.1	-3.2	1.1	-1.0	-1.0

	(19-21)	0.5	1.3	-0.8	1.0	-0.5	-1.4	0.8	-1.1	-1.1
	(31-1)	0.0	0.3	0.6	1.0	0.0	-0.4	-0.7	-1.1	-1.1
	(3-5)	0.4	0.1	0.5	1.0	-0.9	-0.4	-1.3	-2.6	-2.6
	(17-19)	0.8	-0.4	0.6	1.0	-2.2	1.1	-1.8	-3.0	-3.0
	(13-15)	-0.1	0.1	1.1	1.0	0.7	-0.3	-5.4	-5.0	-5.0
	(7-9)	0.9	-0.6	0.7	1.0	-8.1	5.6	-6.3	-8.8	-8.8
	(21-23)	-0.2	0.2	1.0	1.0	-9.7	9.8	46.9	47.1	47.1
stage 3	(11-13)	-0.2	-0.1	1.3	1.0	-1.7	-0.6	9.2	6.9	6.9
	(23-25)	0.9	-0.5	0.7	1.0	2.3	-1.4	1.7	2.6	2.6
	(27-29)	0.0	-0.3	1.3	1.0	0.0	-0.6	2.5	1.8	1.8
	(15-17)	4.7	-2.8	-0.8	1.0	6.3	-3.9	-1.1	1.4	1.4
	(1-3)	-0.3	-0.4	1.7	1.0	-0.3	-0.5	2.1	1.2	1.2
	(29-31)	0.2	-0.5	1.3	1.0	0.2	-0.5	1.3	1.0	1.0

Unilateral atherosclerosis

		$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔVWd				$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔRlu				$\Delta\text{VWd}/\Delta\text{Rlu}$
		ΔINTd	ΔMEDd	ΔADVd	som	ΔINTd	ΔMEDd	ΔADVd	som	
stage 1	(31-1)	-8.6	1.0	8.5	1.0	-0.6	0.1	0.6	0.07	0.07
	(9-11)	-5.9	-6.6	13.6	1.0	-1.5	-1.7	3.4	0.25	0.25
stage 2	(19-21)	0.0	2.2	-1.2	1.0	0.0	-1.0	0.5	-0.45	-0.45
	(5-7)	0.6	0.1	0.3	1.0	-0.6	-0.1	-0.4	-1.16	-1.16
	(15-17)	0.5	-0.5	1.0	1.0	-0.8	0.8	-1.6	-1.65	-1.65
	(7-9)	0.8	-0.3	0.5	1.0	-1.4	0.5	-0.9	-1.84	-1.84
	(23-25)	-0.6	0.9	0.8	1.0	1.3	-1.7	-1.6	-2.03	-2.03
	(3-5)	0.1	0.1	0.7	1.0	-0.3	-0.3	-1.9	-2.50	-2.50
	(27-29)	0.5	0.2	0.2	1.0	-1.4	-0.6	-0.5	-2.57	-2.57
	(11-13)	-0.3	0.1	1.2	1.0	5.4	-1.8	-19.0	-15.44	-15.44
	(25-27)	0.3	-0.5	1.2	1.0	-13.9	25.9	-62.8	-50.77	-50.77
stage 3	(29-31)	-0.3	0.0	1.3	1.0	-91.8	-4.1	435.3	339.40	339.40
	(13-15)	-0.1	-0.1	1.2	1.0	-0.3	-0.4	5.1	4.40	4.40

(21-23)	-1.4	0.3	2.1	1.0	-4.5	1.0	6.5	3.08	3.08
(1-3)	0.0	0.0	1.0	1.0	-0.1	0.1	2.7	2.66	2.66
(17-19)	1.3	-0.8	0.5	1.0	2.0	-1.3	0.8	1.54	1.54

Circumferential atherosclerosis

		$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔVWd				$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔRlu				$\Delta\text{VWd}/\Delta\text{Rlu}$
		ΔINTd	ΔMEDd	ΔADVd	sum	ΔINTd	ΔMEDd	ΔADVd	sum	
stage 1	(15-17)	2.3	-3.0	1.7	1.0	2.0	-2.7	1.5	0.88	0.88
	(7-9)	-5.7	-2.8	9.5	1.0	-1.7	-0.8	2.8	0.29	0.29
	(3-5)	-12.3	-7.2	20.5	1.0	-1.3	-0.8	2.2	0.11	0.11
stage 2	(11-13)	4.5	-1.0	-2.5	1.0	-1.3	0.3	0.7	-0.30	-0.30
	(27-29)	1.8	-0.5	-0.2	1.0	-1.0	0.3	0.1	-0.58	-0.58
	(25-27)	1.1	0.1	-0.2	1.0	-0.8	-0.1	0.1	-0.73	-0.73
	(9-11)	1.1	-0.1	0.0	1.0	-1.2	0.1	0.0	-1.04	-1.04
	(31-1)	0.9	0.1	0.0	1.0	-1.3	-0.1	0.0	-1.46	-1.46
	(1-3)	0.2	1.2	-0.4	1.0	-0.3	-2.0	0.7	-1.64	-1.64
	(23-25)	0.9	0.0	0.2	1.0	-1.6	0.0	-0.3	-1.85	-1.85
	(13-15)	2.0	-1.3	0.3	1.0	-5.7	3.6	-0.7	-2.86	-2.86
	(19-21)	0.2	0.5	0.3	1.0	-1.1	-3.1	-1.6	-5.80	-5.80
	(29-31)	0.1	1.3	-0.4	1.0	-0.7	-7.6	2.3	-5.98	-5.98
	(5-7)	0.0	0.0	1.0	1.0	-0.1	-0.5	-11.0	-11.55	-11.55
	(21-23)	0.6	0.2	0.3	1.0	-9.9	-2.8	-5.0	-17.74	-17.74
stage 3	(17-19)	-0.4	-0.3	1.7	1.0	-1.0	-0.8	4.2	2.40	2.40

Extreme unilateral atherosclerosis

		$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔVWd				$\Delta\text{INTd}/\Delta\text{MEDd}/\Delta\text{ADVd}$ ratio ΔRlu				$\Delta\text{VWd}/\Delta\text{Rlu}$
		ΔINTd	ΔMEDd	ΔADVd	sum	ΔINTd	ΔMEDd	ΔADVd	sum	
stage 2	(5-7)	1.1	0.4	-0.6	1.0	-0.5	-0.2	0.2	-0.42	-0.42
	(9-11)	3.0	-0.4	-1.7	1.0	-1.4	0.2	0.7	-0.45	-0.45
	(1-3)	1.8	-0.2	-0.6	1.0	-1.2	0.2	0.4	-0.68	-0.68
	(7-9)	0.9	0.0	0.0	1.0	-1.1	0.0	0.0	-1.12	-1.12

	(15-17)	1.2	-0.6	0.5	1.0	-1.9	1.1	-0.7	-1.63	-1.63
	(11-13)	2.8	-1.8	0.0	1.0	-5.1	3.3	0.0	-1.83	-1.83
	(19-21)	-52.9	23.8	30.1	1.0	144.2	-64.8	-82.1	-2.72	-2.73
	(3-5)	1.0	0.0	0.0	1.0	-2.8	0.1	-0.1	-2.81	-2.81
	(31-1)	-0.1	0.6	0.6	1.0	0.6	-2.6	-2.7	-4.75	-4.75
	(29-31)	1.6	-0.4	-0.2	1.0	-8.4	2.0	1.2	-5.23	-5.23
	(23-25)	2.8	-1.5	-0.3	1.0	10.6	-5.8	-1.1	3.76	3.76
stage 3	(27-29)	0.0	-0.2	1.2	1.0	0.1	-0.7	4.2	3.60	3.60
	(13-15)	0.0	0.0	1.0	1.0	0.1	0.0	2.2	2.23	2.23
	(21-23)	0.3	-0.3	1.0	1.0	0.6	-0.7	2.1	2.07	2.07
	(25-27)	-0.6	-0.1	1.7	1.0	-1.2	-0.2	3.3	1.90	1.90
	(17-19)	2.3	-1.1	-0.2	1.0	2.7	-1.3	-0.2	1.15	1.15

254 Their summed values in proportion to $\Delta V W d$ and $\Delta R l u$. Triplets are arranged in descending order based on $\Delta R l u$ - $V W d$ trendline a-values. Bold marks the

255 transition from stage 2 to stage 3.

256 Despite semi-range $\Delta INTd$, $\Delta MEDd$, and $\Delta ADVd$ mutually variable interactions, semi-range
 257 ΔVWd was strongly associated with semi-range ΔRlu in a systemic way (Table 8). This
 258 finding emphasizes that semi-ranges reliably reproduce measurement data.

259 **Table 8. Trendline Formula ΔRlu vs. ΔVWd Triplets.**

Normal			
		ΔVWd	
stage 1	(11-13)	-2.9_0.9	$y = 1.1313x + 3.4377$
	(3-5)	-1.3_2.2	$y = 2.0784x - 3.2453$
stage 2	(19-21)	-0.3_1.4	$y = -4.0422x + 1.5327$
	(23-25)	1.4_0.4	$y = -3.6406x + 1.8347$
	(13-15)	-0.1_-0.3	$y = -3.6478x - 0.7137$
	(9-11)	0.1_0.9	$y = -2.8024x + 2.5118$
	(27-29)	0.3_-1.3	$y = -1.154x + 0.2855$
	(21-23)	2.9_-2.5	$y = -0.6874x - 1.0597$
	(17-19)	-2.9_2.4	$y = -0.6823x - 0.3664$
	(7-9)	-3.9_1.3	$y = -0.5714x + 0.1617$
	(1-3)	5.3_3.2	$y = -0.5557x - 0.6603$
	(31-1)	3.5_3.9	$y = -0.3379x - 0.0314$
	(29-31)	2.2_-2.1	$y = -0.0841x + 2.5138$
stage 3	(5-7)	-1.4_3.8	$y = 0.2787x - 0.7202$
	(25-27)	-2.9_-0.5	$y = 0.3951x - 0.2123$
	(15-17)	-1.7_3.0	$y = 0.7638x - 0.1772$
Unilateral atherosclerosis			
		ΔVWd	
stage 1	(31-1)	-0.49_-0.53	$y = 13.702x + 2.9726$
	(9-11)	0_-0.6	$y = 3.9965x - 1.8825$
stage 2	(19-21)	2.2_0.1	$y = -2.2364x + 1.9104$
	(5-7)	-16.1_-8	$y = -0.862x + 4.3621$
	(15-17	7.8_-2.5	$y = -0.6078x - 0.762$
	(7-9)	2_-12	$y = -0.5448x + 5.2015$
	(23-25)	0.5_7.3	$y = -0.4929x + 4.6382$
	(3-5)	5.7_-6	$y = -0.4005x + 1.5525$
	(27-29)	-7.7_5.4	$y = -0.3889x - 5.3733$
	(11-13)	0.6_-7.9	$y = -0.0648x - 1.8162$
	(25-27)	-1.7_8.6	$y = -0.0197x - 7.4485$
stage 3	(29-31)	3_9.5	$y = 0.0029x - 6.7615$
	(13-15)	3.7_-7.7	$y = -0.6042x + 4.3451$
	(21-23)	-2.3_1.1	$y = 0.3251x + 3.8714$
	(1-3)	1_5.5	$y = 0.3765x - 1.6447$

	(17-19)	2_0.2	$y = 0.2272x + 1.2483$
Circumferential enlarged intima			
		ΔVWd	
stage 1	(25-27)	8.4_3.9	$y = 2.0466x - 16.965$
stage 2	(9-11)	-7_-0.6	$y = -1.5447x - 4.3011$
	(5-7)	-2.1_0.6	$y = -1.0458x + 6.2907$
	(19-21)	9.6_1.2	$y = -0.9521x + 9.5283$
	(31-1)	4_4.5	$y = -0.897x + 0.0929$
	(3-5)	6.6_-4.5	$y = -0.3873x + 6.413$
	(17-19)	-0.2_4.3	$y = -2.2438x + 3.6943$
	(13-15)	10.6_-9.8	$y = -0.1984x - 5.6796$
	(7-9)	8.1_-13.9	$y = -0.1138x + 1.5641$
	(21-23)	11_-22	$y = 0.0212x + 6.6839$
stage 3	(11-13)	6.6_-7.4	$y = 0.1446x - 8.8613$
	(23-25)	2.6_-14.4	$y = 0.3841x + 13.374$
	(27-29)	-6.2_6.4	$y = 0.5418x - 8.9512$
	(15-17)	3_6.1	$y = 0.7385x - 7.9461$
	(1-3)	-3.5_1.2	$y = 0.8057x + 5.6836$
	(29-31)	-1.8_4.5	$y = 0.9747x - 9.9709$
Circumferential atherosclerosis			
		ΔVWd	
stage 1	(15-17)	-06_5.0	$y = 1.1368x - 7.2236$
	(7-9)	-4.5_-3.7	$y = 3.4363x + 21.797$
	(3-5)	6.4_6.9	$y = 9.5084x - 59.809$
stage 2	(11-13)	6.0_11.4	$y = -3.3284x + 16.211$
	(27-29)	8.7_-8.3	$y = -1.7298x - 10.409$
	(25-27)	-23_1.1	$y = -1.3753x - 8.3641$
	(9-11)	-49.9_-18.9	$y = -0.966x - 4.8749$
	(31-1)	5.4_6.1	$y = -0.685x + 0.1685$
	(1-3)	8.1_2.9	$y = -0.6085x + 3.0882$
	(23-25)	-37.5_6.7	$y = -0.5403x + 2.927$
	(13-15)	-3.2_7.0	$y = -0.3501x - 10.488$
	(19-21)	21.9_1.1	$y = -0.1724x + 3.1707$
	(29-31)	-1.4_2.4	$y = -0.1673x - 5.2356$
	(5-7)	8.8_-9	$y = -0.0866x + 5.536$
	(21-23)	11.8_-14.9	$y = -0.0564x + 6.3962$
stage 3	(17-19)	4.3_12.6	$y = 0.4158x - 5.6201$
Extreme unilateral atherosclerosis			
		VWd	
stage 2	(5-7)	6.7_-4.3	$y = -2.403x + 16.795$
	(9-11)	11.4_-1.3	$y = -2.2349x - 2.0211$
	(1-3)	4.6_-0.3	$y = -1.464x + 5.0858$
	(7-9)	-81_33	$y = -0.8929x - 2.203$
	(15-17)	0_22.3	$y = -0.6133x - 4.692$

	(11-13)	-7.4_7.3	$y = -0.5475x + 2.9391$
	(19-21)	11.5_10.8	$y = -0.3669x - 3.3153$
	(3-5)	9.9_36	$y = -0.3564x + 12.252$
	(31-1)	-9.4_-10.5	$y = -0.2104x + 0.0782$
	(29-31)	-13.9_-6.2	$y = -0.1912x - 0.2728$
	(23-25)	11.1_5.7	$y = 0.2662x - 4.7889$
stage 3	(27-29)	-21.6_-3.5	$y = 0.2776x + 3.2276$
	(13-15)	7.2_-20.3	$y = 0.4474x - 3.1283$
	(21-23)	-0.6_18.9	$y = 0.4833x - 5.4384$
	(25-27)	2.7_10.7	$y = 0.5251x - 4.5842$
	(17-19)	11.1_20	$y = 0.8697x - 26.254$

Triplets are arranged in descending order based on trendline a-values $\Delta Rlu-VWd$.

Discussion

Excision of pressure perfused vessels is a standard method used to prepare and examine the cardiac vessels at autopsy because it allows better approximation of the *invivo* lumen and vessel wall configuration. However, no agreement has been reached on the best post-mortem vessel examination technique, with wide ranges of perfusion pressures used in different studies making it impossible to compare results. Here, we used non-perfused vessels to better preserve the elastic characteristic of the coronary vessel wall, with residual wall stress clearly evident by the cut ends of the walls moving away from each other after longitudinal incision. Sections cut perpendicular to the longitudinal axis maintain residual wall stress, thereby retaining the basal lumen and vessel wall configuration [7]. This approach preserves the mutual relationships, as confirmed by our results.

In essence, the main basic process is the ‘counter-balancing’ system: growth of $\Delta INTd$, $\Delta MEDd$, or $\Delta ADVd$ counter-balanced by the other two. As such, these are functionally united in a direct way ($\Delta FU-1$). This basic function stays intact regardless of vessel wall pathology, though triplets present the same sign in a minority of sections. In an indirect way $\Delta INTd$,

ΔMEDd , and ΔADVd determine the course of ΔVWd in every triplet (increasing or decreasing), its measure by semi-range values and their sign change.

Within each section, stages are defined in which the mutual relationship between ΔVWd and ΔRlu changes, from an increase in ΔVWd and increased ΔRlu (stage 1 and stage 3) to a decrease in ΔRlu and increased ΔVWd (stage 2). The transition of stage 1 to stage 2 is marked by trendline a-value $\Delta\text{VWd} = 0$ and $\Delta\text{Rlu} = 1$, whereas the transition from stage 2 to stage 3 is marked by a-value $\Delta\text{VWd} = 1$ and $\Delta\text{Rlu} = 0$. The a-value $\Delta\text{VWd} = 0$ and $\Delta\text{Rlu} = 0$ reflect the peak/bottom parabola values before data transition to Δ values, which transforms a parabolic course to a linear course. As such, stages are defined by the ΔVWd and ΔRlu parabolic course remnants, a change from synchronic (same trendline a-value sign, stages 1 and 3) to asynchronous (opposite trendline sign, stage 2). This proves that the $\Delta\text{VWd}/\Delta\text{Rlu}$ relationship is course- and sign-dependent and, therefore, independent of their values in absolute terms.

Atherosclerotic and non-atherosclerotic sections cannot be differentiated by triplet behavior. For example, ΔINTd growth with atherosclerosis is marked only by a shift from stage 1 to stage 3. This illustrates that even atherosclerotic sections exhibit an increase in ΔRlu in relation to ΔVWd growth, which implies independence from vessel wall constitution. Support for this view is given by the summed semi-range values ΔINTd , ΔMEDd , and ΔADVd in proportion to semi-range ΔRlu , which is similar to the $\Delta\text{VWd}/\Delta\text{Rlu}$ ratio in absolute terms. Therefore, the atherosclerotic coronary vessel wall cannot be considered inert, but still proves to be a well-adapting ‘organ’.

The ΔRlu course is entirely dependent on the ΔVWd course, but their relationship is only consistent within each triplet and, as such, variable between different triplets. Consequently, the ΔVWd has a dissimilar course within each singular triplet, indicating that the quest for a

specific coronary vessel wall dimension as parameter of ‘physiological’ or ‘pathological’ is futile. The same is valid for the intima, media, and adventitia dimensions. Both course-determining factors prove the existence of a strict control mechanism active within all sections and un-altered by the atherosclerotic process.

Successive events describe a system’s course, which is artificial in regards to non-consecutive triplets within each section. This added to the finding that consecutive sections resemble each other only roughly (not shown), assuming systems processes are active throughout the vessel wall. If and how the control mechanism functions in a longitudinal way should be revealed by further investigation.

Overall, the findings indicate that basic systems and mechanisms are un-altered by the atherosclerotic process, which makes a systemic defect as the cause of atherosclerosis less probable and a superposed agent (e.g., inflammation) more plausible. The constituent parts of the coronary vessel wall (intima, media, adventitia) act as a true functional unit via a counterbalancing system and cannot be considered as representative of the coronary vessel wall pathology. If this is also the case with elastic arteries, such as the carotid arteries, using the intima/media ratio as a parameter of coronary artery pathology could be debatable [8, 9]. The stages observed in every section could instigate reconsideration of the cause of coronary artery remodeling [10].

Atherosclerosis is an umbrella term for a process in which plaques are ultimately formed. The aorta appears more ulcerative (craters) than the coronary arteries and the processes leading to these differences uncertain. Therefore, findings on coronary atherosclerotic processes cannot be considered normative for the aortic processes. Differences could exist between muscular and elastic arteries, or even between different muscular or elastic arteries. This is illustrated

by the coronary arteries initially lacking the sub-endothelial (intimal) layer, in contrast to cerebral arteries initially lacking the adventitial layer, making them translucent *in vivo*. Therefore, our study is only the first step in understanding the process from arterial physiology to pathology. Further investigation of different arteries (single sections and section series) could elucidate similarities and/or differences. The random systemic sampling technique could aid in obtaining results for comparisons.

Conflict of interest: none

References

1. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1995;92: 1355-1374.
2. Stary HC, Chandler AB, Glagov S, Guyton JR, Insull W, Rosenfeld ME, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee an Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol*. 1994;14: 840-856.
3. Herrmann J, Lerman A. Coronary artery disease: development and progression. In: Barsness GW, Holmes DR, editors. *Coronary artery disease*. London: Springer; 2012. pp. 21-28.
4. Stary HC, Blankenhorn DH, Chandler AB, Glagov S, Insull W, Richardson M, et al. A definition of the intima of human arteries and its atherosclerosis-prone regions. A report from

346 the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart
347 Association. *Circulation*. 1992;85: 391-405.

348 5. Schwartz SM, Blois de D, O'Brien RM. The Intima: Soil for atherosclerosis and
349 restenosis. *Circ Res*. 1995;77: 445-465.

350 6. De Groot P, Veldhuizen RW. Human coronary artery remodeling, beginning and end
351 of the atherosclerotic process. *PLoS One*. 2006;1: e91.

352 7. Humphrey JD. Cardiovascular solid mechanics, cells, tissues, and organs. London:
353 Springer; 2010.

354 8. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with intima-media
355 thickness, more accurately predicts coronary artery disease events: A meta-analysis.
356 *Atherosclerosis*. 2012;220: 128-133.

357 9. Amato M, Montorsi P, Ravani A, OldaniStefano E, et al. Carotid intima-media
358 thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with
359 quantitative coronary angiography and intravascular ultrasound findings. *Eur Heart J*.
360 2007;28: 2049-2050.

361 10. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human
362 atherosclerotic coronary arteries. *New Engl J Med*. 1987;316: 1371-1375.

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Figure

A

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doos 70, nr.56

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B

Section "normal".

C

Section "normal".

Figure

Figure

Figure

Figure