MEDICAL UNIVERSITY "PROF. PARASKEV STOYANOV" OF VARNA
DEPARTMENT OF SURGERY
CLINIC OF CARDIAC SURGERY

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POSSIBILITIES OF TRANSIT-TIME FLOWMETRY FOR INTRAOPERATIVE BLOOD FLOW OBJECTIFICATION AND COMPARISON IN CORONARY SURGERY ON A 'BEATING HEART' AND WITH EXTRACORPOREAL CIRCULATION

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ABBREVIATIONS USED

AP	angina pectoris
ECC	extracorporeal circulation
IHD	ischemic heart disease
BMI	body mass index
CAB	coronary artery bypass
CPB	cardiopulmonary bypass
CT	computed tomography
PCI	percutaneous coronary intervention
EF	ejection fraction
CAIE	chronic arterial insufficiency of the extremities
COPD	chronic obstructive pulmonary disease
CK-MB	creatine kinase-muscle/brain
NYHA	New York Heart Association
SPECT	single-photon emission computer tomography

1. INTRODUCTION

Recently, socially significant diseases worldwide such as ischemic heart disease (IHD), arterial hypertension and cardiac arrhythmias continue to be leading causes for disability and death of the population. Despite the undoubted achievements of prevention, diagnosis and management, the results do not remain so optimistic as one could expect.

Along with modern drug therapy of IHD, uninterruptedly perfectioned surgical methods enter on a mass scale the world practice. After its introduction in the beginning of the 70es of the last century, coronary arterial bypass (CAB) has been rapidly established as a method for operative treatment of advanced coronary artery disease. Along with the conventional method with extracorporeal circulation (ECC), in many countries, particularly in Easthern Europe, CAB on a 'beating heart' is more and more intensively applied.

The issues of pre- and intraoperative diagnosis of the status of the coronary circulation and coronary artery bypass grafting come to the forefront. Coronary angiography has been established as a golden standard in this respect, however, during the recent two decades, the new diagnostic method, i. e. transit-time flowmetry of blood flow through the anastomosis of the bypass graft becomes more and more popular, too.

In our country, there are no investigations of the clinical application of this method yet, although numerous publications by foreign authors are devoted to this topic testifying to the advantages of the intraoperative transit-time flowmetry in terms of the early and precise diagnosis of graft dysfunction and determining the necessity of timely operative revision. In our Clinic of Cardiac Surgery, approximately 40% of the coronary interventions are performed on a 'beating heart'. The principal opponents of this technique emphasize as an disadvantage the possibility for incorrect anastomosis accomplishment because the presence of a mobile operative field and the need for acquisition of specific technical skills when performing the graft on a 'beating heart'. One accepts that these factors lead to incomplete revascularization and long-term survival reduction. During the recent years, new instruments for heart stabilization in the graft area entered cardiac surgery. In our opinion, this circumstance as well as the usage of intracoronary shunts warranting the perfusion during the graft procedure and the presence of numerous interventions on a 'beating heart' minimize the possibility for incorrect anastomosis accomplishment with this type of myocardial revascularization technique.

All of this has stimulated us to carry out the present complex investigation of the applicability of transit-time flowmetry for the intraoperative blood flow objectification and comparison in conventional CAB and CAB a 'beating heart'.

2. PURPOSE AND TASKS

The purpose of the present dissertation is to analyze the possibilities of intraoperative transit-time flowmetry for early objective evaluation of the coronary blood flow and optimization of the surgical behaviour in IHD patients.

The following tasks have been defined for performing this purpose:

1. To juxtapose the values of coronary blood flow, pulsatile index and wave morphology as assessed by means of intraoperative transit-time flowmetry in the surgically treated patients.
2. To analyze the correlation dependences between blood flow and pulsatile index in arterial and venous grafts in both operation types.
3. To juxtapose the values of cardiac troponin and CK-MB in the patients surgically treated with conventional CAB and those treated with CAB on a 'beating heart'.
4. To juxtapose the values of pre- and postoperative left ventricular ejection fraction (EF) and the duration of both interventions in the patients surgically treated with conventional CAB and those treated with CAB on a 'beating heart'.
5. To identify the diagnostic significance of the intraoperative transit-time flowmetry when optimizing the behaviour in the patients having undergone conventional CAB and CAB on a 'beating heart'.
6. To compare the operative results and draw conclusions about the efficacy of the protocol for operative method selection, i.e. CAB on a 'beating heart' or conventional CAB applied by us.

WORKING HYPOTHESIS

The usage of the method of intraoperative transit-time flowmetry could help the timely diagnosis of coronary graft dysfunction and substantiate the purposeful subsequent therapeutic behaviour in IHD patients having undergone conventional CAB and CAB on a 'beating heart'.

3. MATERIAL AND METHODS

3.1. Material

During the period between January 1, 2014 and December 31, 2017, a total of 971 patients with isolated IHD were operated on in the Clinic of Cardiac Surgery at St. Marina University Hospital of Varna. The present investigation covers a total of 143 patients. It deals with 111 males at a mean age of 63,29±9,78 years (range, 38 to 84 years) and 32 females at a mean age of 66,43±9,58 years (range, 49 to 81 years) (Figure 1). They were operated on during the period between January 1, 2014 and December 31, 2017.

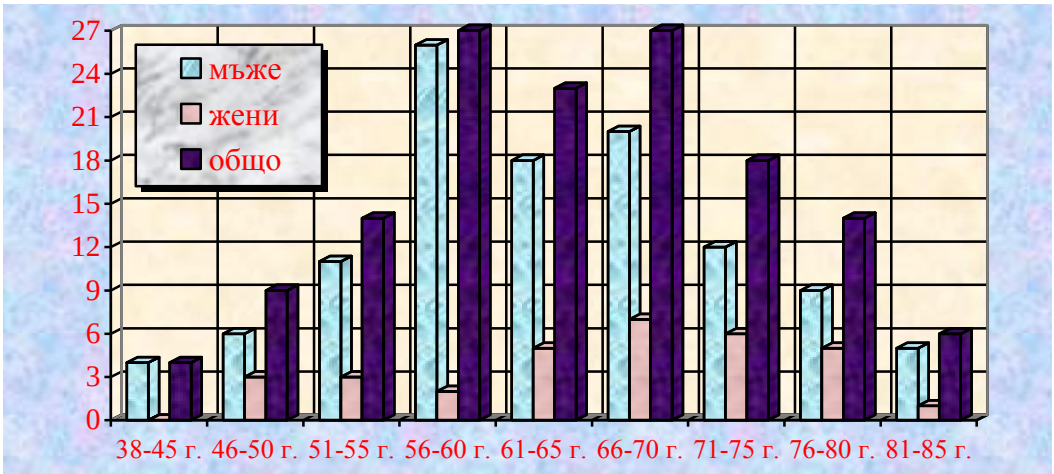

Figure 1. Patients' distribution according to sex and age groups

In 79 of the patients (in 55,24%) CAB on a 'beating heart' (off-pump) was performed, while in the rest 64 ones (44,76% of the cases) a conventional CAB with ECC (on-pump) was done. Annual dynamics of the number of the patients operated on accordiong to sex is demonstrated on Figure 2 but that according to the method used is shown on Figure 3.

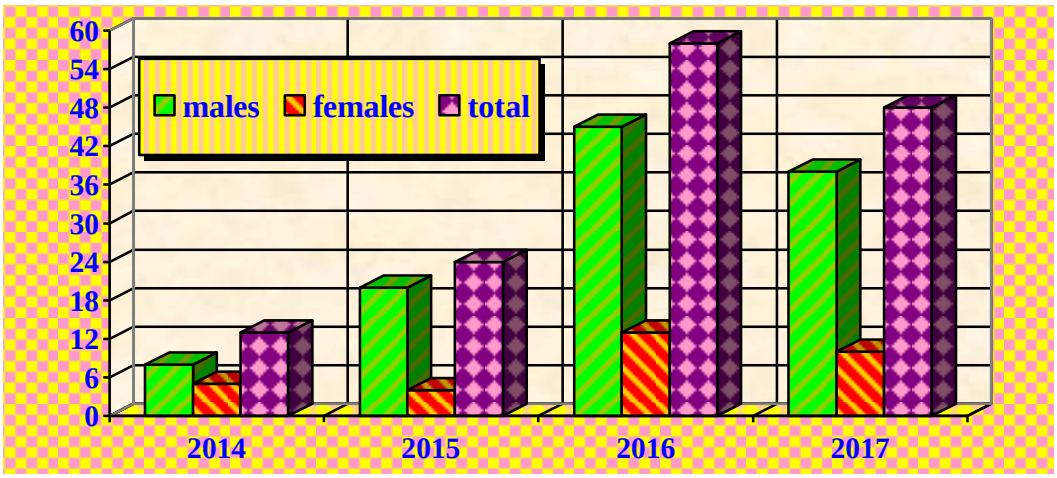

Figure 2. Patients' distribution according to sex and year of surgery

Patients' distribution according to the diagnosis of the main disease and surgical method used is systematized in Table 1 while that according to the number of accompanying diseases is done in Table 2.

Table 1. Application of off-pump and on-pump methods
in patients with a different diagnosis of the disease

Diagnosis	on-pump		off-pump		total	
	n	%	n	%	n	%
Single-vessel disease	0	0	4	0	4	2,79
Single-vessel disease+left main stenosis	2	1,40	1	0,70	3	2,10
Two-vessel disease	5	3,50	7	4,90	12	8,39
Two-vessel disease+left main stenosis	2	1,40	9	6,29	11	7,69
Two-vessel disease+aortic valve stenosis	1	0,70	0	0	1	0,70
Three-vessel disease	35	24,48	44	30,77	79	55,24
Three-vessel disease+left main stenosis	14	9,79	14	9,79	28	19,58
Three-vessel disease+aortic valve stenosis	4	2,79	0	0	4	2,79
Three-vessel disease+left main stenosis +mitral valve insufficiency	1	0,70	0	0	1	0,70
total	64	44,76	79	55,24	143	100

Table 2. Patients' distribution according to the number of accompanying diseases

Number of diseases	on-pump		off-pump		total	
	n	%	n	%	n	%
0	2	3,12	4	5,06	6	4,20
1	28	43,75	40	50,63	68	47,55
2	19	29,69	22	27,85	41	28,67
3	6	9,38	11	13,92	17	11,89
4	8	12,50	1	1,27	9	6,29
5	1	1,56	1	1,27	2	1,40
total	64	100,00	79	100,00	143	100,00

3.2. Methods

The distributions of the male and female patients during the period of investigation according to their number in off-pump- and on-pump-operation can be seen in Table 3 and Table 4.

Table 3. Distribution in off-pump-operation according to patients' sex

Year	males		females		total	
	n	%	n	%	n	%
2014	-	-	3	23,08	3	3,80
2015	10	15,15	-	-	10	12,66
2016	35	53,03	4	30,78	39	49,37
2017	21	31,82	6	46,15	27	34,18
total	66	100	13	100	79	100

Table 4. Distribution in on-pump-operation according to patients' sex

Year	males		females		total	
	n	%	n	%	n	%
2014	8	17,78	2	10,53	10	15,63
2015	10	22,22	4	21,05	14	21,88
2016	10	22,22	9	47,37	19	29,69
2017	17	37,78	4	21,05	21	32,81
total	45	100	19	100	64	100

The distruibution of the patients operated on in whom control angiographies have been performed at least six months after the surgical intervention according to sex and method used is illustrated on Figure 3.

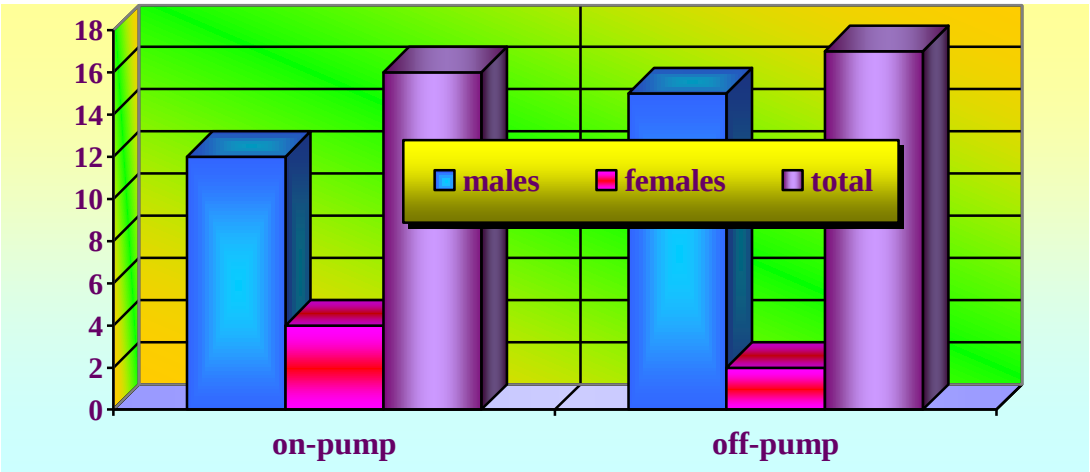

Figure 3. Distribution of the patients with control angiographies according to sex and method used

The distruibution of the arterial and venous grafts in the patients with CAB on a 'beating heart' and conventional CAB is juxtaposed in Table 5.

The general scheme of the operative interventions in our patients is presented on Figure 4.

Between one and five arterial grafts are placed in 41 patients (in 98,60%) but between one and four venous grafts are done in 80 patients (in 55,94% of the cases). The mean number of the arterial grafts per patient is 2,204±1,114 and that of the venous one is 1,138±1,153.

Patient's distributions according to the number of the arterial and venous grafts and operative method used are summarizerd in Table 6 and Table 7.

Table 5. Number of arterial and venous grafts in patients with CAB on a ‘beating heart’ and conventional CAB

CAB on a ‘beating heart’			conventional CAB		
Graft	Target artery	n=235	Graft	Target artery	n=226
LIMA	LAD	78	LIMA	LAD	61
LIMA	Dg	13	LIMA	Dg	2
LIMA	RIM	1	LIMA	RIM	1
RIMA	Rcx	48	LIMA	Rcx	1
RIMA	Dg	10	RIMA	Rcx	25
RIMA	RIM	9	RIMA	Dg	13
RIMA	RCA	22	RIMA	RIM	3
v.s.m.	Rcx	21	RIMA	RCA	9
v.s.m.	RCA	24	RIMA	LAD	1
v.s.m.	Dg	6	RA	DG/RCA/Rcx	15
v.s.m.	RIM	2	v.s.m.	Rcx	39
v.s.m.	LAD	1	v.s.m.	RCA	44
			v.s.m.	Dg	7
			v.s.m.	RIM	2
			v.s.m.	LAD	3

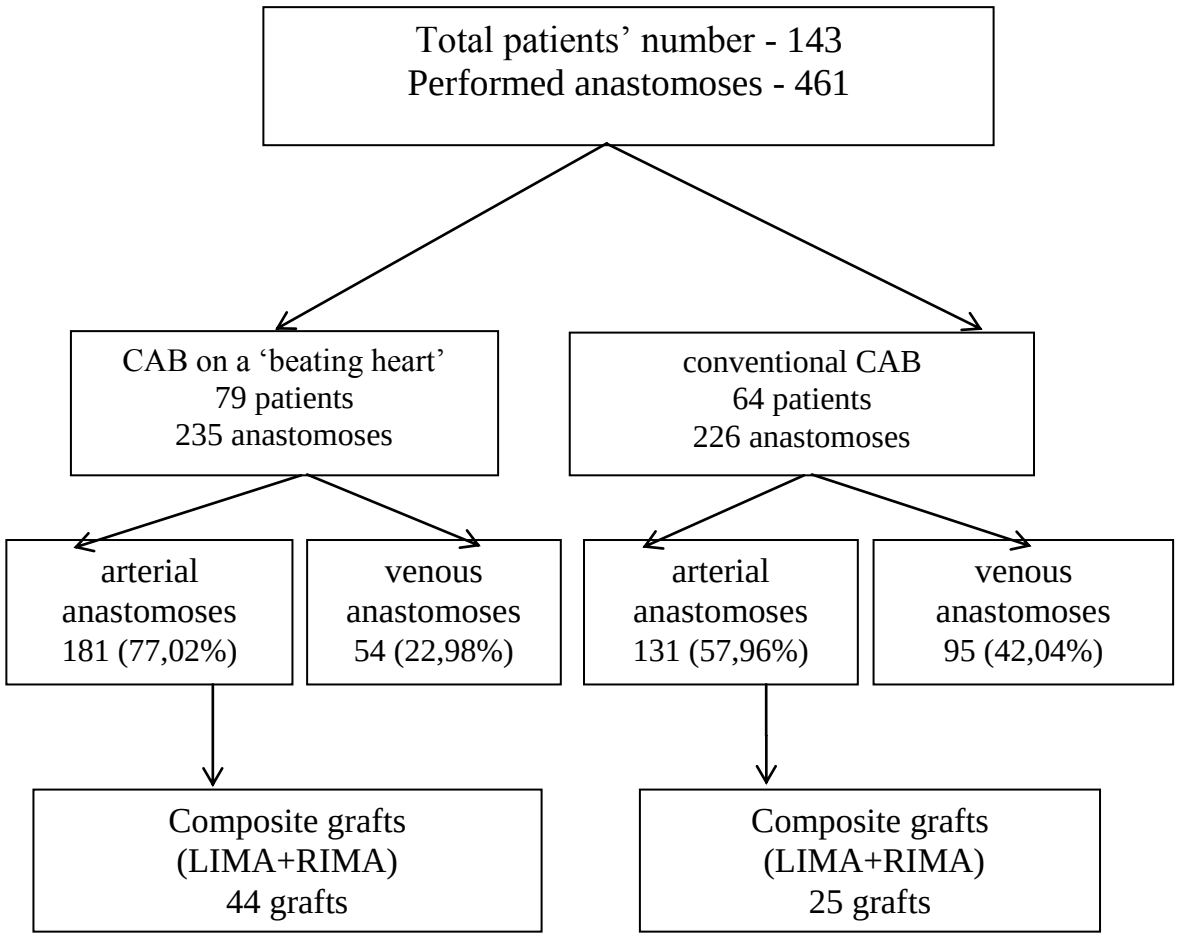

Figure 4. A general scheme of the operative interventions

Table 6. A summarized patients'distribution according to the number of the arterial grafts and operative method used

Number of grafts	on-pump		off-pump		total	
	n	%	n	%	n	%
0	2	3,13	0	0	2	1,40
1	29	45,31	23	29,11	52	36,36
2	8	12,50	18	22,78	26	18,18
3	15	23,44	29	36,71	44	30,77
4	10	15,62	8	10,13	18	12,59
5	0	0	1	1,27	1	0,70
total	64	100,00	79	100,00	143	100,00

Table 7. A summarized patients'distribution according to the number of the venous grafts and operative method used

Number of grafts	on-pump		off-pump		total	
	n	%	n	%	n	%
0	16	25,00	47	59,49	63	44,06
1	18	28,13	18	22,79	36	25,17
2	16	25,00	8	10,13	24	16,78
3	10	15,62	6	7,59	16	11,19
4	4	6,25	0	0	4	2,80
total	64	100,00	79	100,00	143	100,00

Patient's distribution according to the number of anastomoses and operative method used is demonstrated in Table 8.

Table 8. Patients'distribution according to the number of the anastomoses and operative method used

Number of anastomoses	on-pump		off-pump		total	
	n	%	n	%	n	%
1	0	0	7	8,86	7	4,89
2	8	12,50	12	15,19	20	13,99
3	23	35,94	40	50,63	63	44,06
4	24	37,50	16	20,25	40	27,97
5	9	14,06	4	5,07	13	9,09
total	64	100,00	79	100,00	143	100,00

We make use of the following operative techniques:

i) conventional CAB

ii) CAB on a 'beating heart'

iii) minimally invasive CAB (MIDCAB)

We define a protocol for bilateral preparation of the internal thoracic arteries in patients with multuiple arterial grafts and another protocol for restriction of the

development of sternotomy wound infections after the bilateral preparation of the internal thoracic arteries by elaborating and approving the algorithm for accomplishment of the intraoperative transit-time flowmetry with the purpose for repeatedly measurement of blood flow and pulsatile index and characterization of coronary graft wave morphology in our patients. Based on these flowmetric data, we define the indications for timely graft revision.

We present data about the number of damaged and revascularized arteries as well as from left ventricular EF examinations at patient's admission and discharge from hospital; duration of the various types of operative intervention, including time of cardiopulmonary bypass (CPB) and aorta cross-clamping time; blood flow volumes in the arterial and venous grafts and pulsatile index in the arterial and venous grafts.

We perform examinations of CK-MB and cardiac troponin-I by routine methods in all the patients operated on. The reference values of CK-MB and cardiac troponin-I in the Clinical Laboratory at St. Marina University Hospital of Varna are 2-25 IU/L and 0,20-0,32 ng/mL, respectively. Data from the examinations are statistically processed and presented in tables.

We analyze the correlation dependences between the operative, haemodynamic and laboratory parameters in our patients.

We use the following statistical methods for analysis and interpreration of the data obtained: descriptive methods such as alternative and variation analysis, methods for hypothesis check such as Student-Fisher *t*-test and χ^2 Pearson coefficient, correlation analysis and graphic analysis. Statistical data are processed by using IBM SPSS software package, version 23.

4. OWN RESULTS

4.1. Analysis of operative parameters

The results from pre- and postoperative EF examinations in the patients who have undergone both types of operations are summarized in Table 9 and Table 10.

Table 9. Distribution of EF values (in percentage) in the patients prior to and after surgery

period of examination/method of operation	n	minimal value	maximal value	mean value	standard deviation
prior to operation/on-pump	64	29,00	76,00	50,875	10,815
prior to operation /off-pump	79	22,00	76,00	50,532	12,012
after operation/on-pump	61	30,00	74,00	52,049	11,151
after operation/off-pump	79	25,00	70,00	51,114	9,999
total preoperative/at admission	143	22,00	76,00	50,685	11.453
total postoperative/at discharge	140	25,00	74,00	51,521	10,488

Table 10. Distribution of EF values (in percentage) in the male and female patients prior to and after surgery

Examined patients	n	period of examination/method of operation			
		minimal value	maximal value	mean value	standard deviation
		prior to operation/on-pump			
males	45	29,00	70,00	49,667	10,405
females	19	32,00	76,00	53,737	11,508
		prior to operation/off-pump			
males	66	22,00	76,00	49,833	11,354
females	13	28,00	71,00	54,077	14,941
		after operation/on-pump			
males	43	30,00	70,00	51,837	11,002
females	18	31,00	74,00	52,556	11,808
		after operation/off-pump			
males	66	25,00	70,00	51,091	9,590
females	13	30,00	66,00	51,231	12,316

The results from the examination of the duration of surgery in on-pump and off-pump-operations in all the patients are presented in Table 11 and Table 12.

Table 11. Operation time values in on-pump operation (in min.) in all the patients

Operation time	n	minimal value	maximal value	mean value	standard deviation
total duration	61	170,00	560,00	322,459	78,526
CPB duration	63	48,00	334,00	120,556	52,313
Aorta cross-clamping duration	63	22,00	227,00	71,619	31,767

Table 12. Mean values of operation time in off-pump operation (in min.) in all the patients

Patients operated on	n	Operation time			
		minimal value	maximal value	mean value	standard deviation
males	66	115,00	410,00	268,106	51,774
females	13	155,00	350,00	261,538	69,203
total	79	115,00	410,00	267,025	54,558

The results from the examination of the duration of surgery in on-pump and off-pump-operations according to the number of grafts in all the patients are presented in Table 13 and Table 14.

Table 13. Duration of on-pump-operation (in minute intervals) depending on the number of grafts in all the patients

Number of grafts	Duration									
	170-210		271-370		371-470		471-560		total	
	n	%	n	%	n	%	n	%	n	%
2	3	4,92	4	6,56	0	0	0	0	7	11,48
3	5	8,20	11	18,03	4	6,56	3	4,92	23	37,70
4	5	8,20	14	22,95	2	3,28	2	3,28	23	37,70
5	2	3,28	4	6,56	2	3,28	0	0	8	14,12
total	15	24,59	33	54,10	8	14,11	5	8,20	61	100,00

Table 14. Duration of off-pump-operation (in minute intervals) depending on the number of grafts in all the patients

Number of grafts	Duration							
	115-215		216-315		316-410		total	
	n	%	n	%	n	%	n	%
1	5	6,33	2	2,53	0	0	7	8,86
2	3	3,80	10	12,66	0	0	13	16,46
3	2	2,53	30	37,98	6	7,59	38	48,10
4	0	0	11	13,92	6	7,59	17	21,52
5	0	0	1	1,27	3	3,80	4	5,06
total	10	12,66	54	68,35	15	18,99	79	100,00

The minimal and maximal durations of on-pump-operation in all the patients are 170,00 and 560,00 min., respectively. The minimal and maximal durations of off-pump-operation in all the patients are 115,00 and 410,00 min., respectively. The results from ANOVA indicate statistically significant differences between the different number of grafts used in terms of the average duration of off-pump-operation only (F=16,180; p=0,0001).

4.2. Analysis of haemodynamic parameters

4.2.1. *Blood flow analysis in arterial and venous grafts in on-pump- and off-pump-operations*

Blood flow values (in mL/min.) in arterial and venous grafts in both types of operation are juxtaposed in Table 15.

The number and relative share of the patients according to blood flow in the arterial grafts in on-pump- and off-pump-operations can be seen in Table 16 and Table 17.

The number and relative share of the patients according to blood flow in the venous grafts in on-pump- and off-pump-operations can be seen in Table 18 and Table 19.

Table 15. Distibution of blood flow values (in mL/min.) in the grafts in on-pump- and off-pump-operations in all the patients

Grafts	n	value/method of operation			
		minimal value	maximal value	mean value	standard deviation
		on-pump			
arterial	131	9,00	88,00	36,717	19,188
venous	95	4,00	99,00	32,185	18,176
		off-pump			
arterial	181	3,00	84,00	26,555	14,751
venous	54	4,00	57,00	23,089	10,361

Table 16. Number and relative share of the patients according to blood flow in the arterial grafts in on-pump-operations

Blood flow (in mL/min.)	males		females		total	
	n	%	n	%	n	%
9-19	9	20,00	4	21,05	13	20,312
20-30	13	28,89	4	21,05	17	26,56
31-40	5	11,11	2	10,53	7	10,94
41-50	8	17,78	6	31,58	14	21,88
51-60	3	6,67	1	5,26	4	6,25
61-70	2	4,44	2	10,53	4	6,25
71-88	5	11,11	0	0	5	7,81
total	45	100,00	19	100,00	64	100,00

Table 17. Number and relative share of the patients according to blood flow in the arterial grafts in off-pump-operations

Blood flow (in mL/min.)	males		females		total	
	n	%	n	%	n	%
3-19	15	23,08	5	35,71	20	25,32
20-30	23	35,38	6	42,86	29	36,70
31-40	18	27,69	0	0	18	22,78
41-50	6	9,23	2	14,29	8	10,13
51-60	1	1,54	0	0	1	1,27
61-70	1	1,54	1	7,14	2	2,53
71-88	1	1,54	0	0	1	1,27
total	65	100,00	14	100,00	79	100,00

The difference between male and female patients concerning the mean blood flow values in the venous grafts is statistically significant in favour of the males (Pearson correlation coefficient χ^2 =11,410 and p≤0,022 while r=-0,310 and p=0,001).

Table 18. Number and relative share of the patients according to blood flow in the venous grafts in on-pump-operations

Blood flow (in mL/min.)	males		females		total	
	n	%	n	%	n	%
4-19	13	29,55	3	15,79	16	25,40
20-30	8	18,18	7	36,84	15	23,81
31-40	9	20,45	7	36,84	16	25,40
41-50	6	13,64	0	0	6	9,52
51-60	4	9,09	2	10,53	6	9,52
61-70	3	6,82	0	0	3	4,76
81-99	1	2,27	0	0	1	1,59
total	44	100,00	19	100,00	63	100,00

Table 19. Number and relative share of the patients according to blood flow in the venous grafts in off-pump-operations

Blood flow (in mL/min.)	males		females		total	
	n	%	n	%	n	%
4-19	16	42,11	1	14,28	17	37,78
20-30	15	39,47	3	42,86	18	40,00
31-40	5	13,16	3	42,86	8	17,78
41-57	2	5,26	0	0	2	4,44
total	38	100,00	7	100,00	45	100,00

4.2.2. *Analysis of pulsatile index in arterial and venous grafts in on-pump- and off-pump-operations*

Pulsatile index values in arterial and venous grafts in both types of operation are juxtaposed in Table 20.

Table 20. Distibution of pulsatile index values in the grafts in on-pump- and off-pump-operations in all the patients

Grafts	n	value/method of operation			
		minimal value	maximal value	mean value	standard deviation
		on-pump			
arterial	131	0,30	5,80	2,42	1,05
venous	95	0,70	20,00	2,76	2,49
		off-pump			
arterial	181	1,20	16,30	3,21	1,59
venous	54	1,20	11,90	3,26	2,03

Pulsatile index values in arterial and venous grafts in on-pump- and off-pump-operations can be seen in Table 21 and Table 22.

Table 21. Pulsatile index values in arterial grafts in on-pump- and off-pump-operations

method of operation	n	mean value	standard deviation	standard error of the mean value
on-pump	64	2,444	1,097	0,137
off-pump	79	2,981	1,040	0,117

There is a statisticallty significant difference between both methods in terms of pulsatile index in the arterial grafts (p=0,003).

Table 22. Pulsatile index values in venous grafts in on-pump- and off-pump-operations

method of operation	n	mean value	standard deviation	standard error of the mean value
on-pump	64	2,763	1,771	0,336
off-pump	79	3,486	2,064	0,505

The individual values of the blood flow (in mL/min.) and pulsatile index in problems-raising grafts identified by means of transit-time flowmetry prior to and after their revision are presented in Table 23 and Table 24.

Table 23. Blood flow (in mL/min.) and pulsatile index in problems-raising grafts prior to and after their revision in on-pump-operations

Patient	Sex	Graft	Target vessel	prior to revision		after revision	
				blood flow	pulsatile index	blood flow	pulsatile index
V.M.	female	v.s.m.	OM1	3	46	16	2,1
Yu.O.	male	LIMA	LAD	2	12,8	40	2,2
M.I.	female	LIMA	LAD	8	21	21	2,7
N.S.	male	v.s.m.	RCA-Pd	10	10,9	32	4,3
		v.s.m.	OM1	9	8,7	37	3,6
D.H.	female	LIMA	LAD	3	21,7	16	2,5
P.S.	male	LIMA	LAD	2	13,2	27	2,3
D.I.	female	LIMA	LAD	3	15	34	2,2
M.Zh.	male	RIMA	OM1	6	21,9	26	1,8
		LIMA	LAD	6	5,9	30	1,3
S.S.	male	LIMA	LAD	1	20	25	2,1
		LIMA	Dg	0	57,6	36	1,8

Table 24. Blood flow (in mL/min.) and pulsatile index in problems-raising grafts prior to and after their revision in off-pump-operations

Patient	Sex	Graft	Target vessel	prior to revision		after revision	
				blood flow	pulsatile index	blood flow	pulsatile index
V.S.	male	RIMA	RCA	2	28,7	4	20
F.Yu.	male	LIMA	LAD	1	16	9	4,2
V.A..	female	LIMA	LAD	1	26,6	8	4,4
S.H.	male	v.s.m.	RCA	4	10	38	3,5

Postoperative alterations of individual values are manifested by a strong blood flow elevation and a strong pulsatile index diminution as objective proof of the effectiveness of the surgical treatment.

4.3. Analysis of laboratory parameters

Mean cardiac troponin-I values in both surgical methods are juxtaposed in Table 25.

Table 25. Cardiac troponin-I values in on-pump- and off-pump-operations

method of operation	n	mean value	standard deviation	standard error of the mean value
on-pump	64	27,066	48,561	6,218
off-pump	79	3,730	8,610	0,969

There is a statistically significant difference between both methods as higher mean cardiac troponin-I values are observed in the patients with on-pump intervention (t=4,191; p=0,0001).

Mean CK-MB values in both surgical methods are juxtaposed in Table 26.

Table 26. CK-MB values in on-pump- and off-pump- operations

method of operation	n	mean value	standard deviation	standard error of the mean value
on-pump	64	89,492	103,749	13,284
off-pump	79	33,342	20,224	2,275

There is a statistically significant difference between both methods as higher mean CK-MB values are observed in the patients with on-pump intervention (t=4,701; p=0,0001).

4.4. Clinical case reports

We illustrate the significance of contemporary intraoperative transit-time flowmetry for the identification of the coronary graft dysfunction and adequate behaviour in two patients with a main diagnosis of IHD.

1. The patient D.B.H, 51-years old, presents with the diagnosis of IHD, effort angina pectoris of III class after NYHA, chronic inferior myocardial infarction, multivesel coronary artery disease, state after OM2 stenting using drug-eluting stent as well as with the following accompanying diseases: arterial hypertension at stage III and of moderate degree, type 2 diabetes mellitus and gout. CK-MB value is 49 IU/L and cardiac troponin-I one is 9,7 ng/mL. By means of coronary angiography, a stenosis of the left anterior descendent artery of 90%, two stenoses of 75% each in the middle segment as well as diffuse lesions up to 50% in OM1, occlusion of OM2, a long proximal stenosis of the right coronary artery of 60% and a stenosis of PL of 95% are established. Echocardiographically, EF of 53% is established at admission and of 57% at discharge from hospital. Surgical treatment includes CAB on a 'beating heart' of three coronary arteries (arterial graft as LAD-LIMA and two venous grafts as OM1>Dg1 - v.s.m. sequential graft). The coronary blood flow in the sequential anastomosis of the venous graft with Dg is 3 mL/min., in the distal anastomosis of the venous graft with OM1, it is 5 mL/min., while the pulsatile index is 4,6 and 1,2, respectively. On Figure 4 and Figure 5, the low blood flow volume through the venous graft towards Dg and OM1 can be seen.

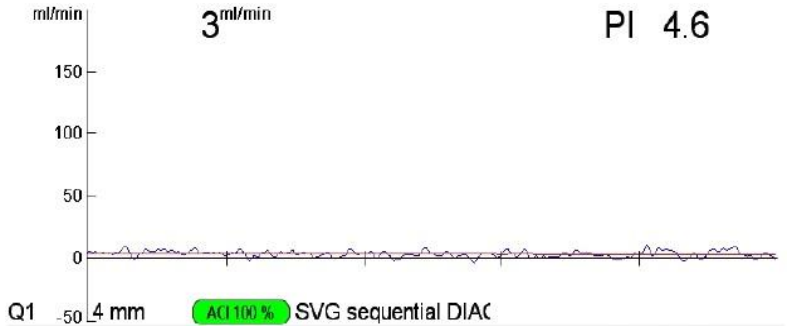

Figure 4. Absent blood flow curve. Low blood flow volume but upper-limit pulsatile index in the sequential anastomosis of the venous graft with Dg

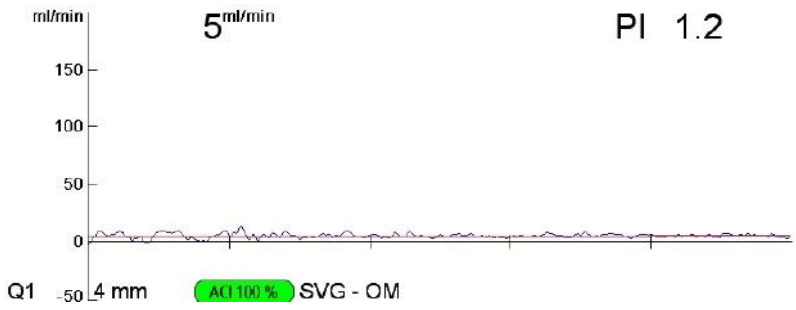

Figure 5. Absent blood flow curve. Low blood flow volume but low pulsatile index in the distal anastomosis of the venous graft with OM1

We apply papaverine solution intraluminally into the venous graft and repeat the examinations. A normalization of the values of the flowmetric parameters is established as the coronary blood flow through the sequential graft to Dg is 23 mL/min. and in the distal anastomosis to the OM1, it is 19 mL/min. Pulsatile index values are 3,9 and 2,8, respectively (Figure 6 and Figure 7).

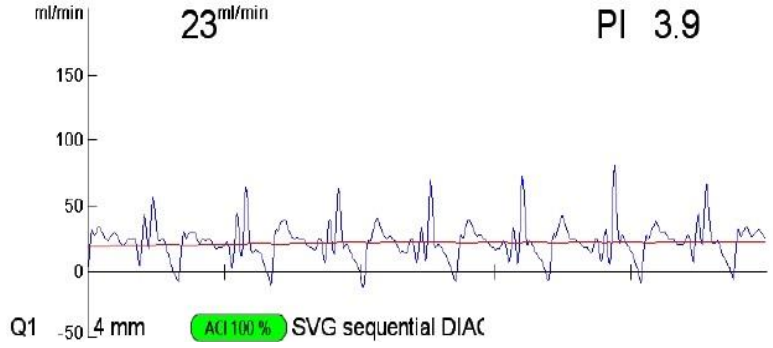

Figure 6. Presence of distal blood flow. A considerable blood flow increase with preservation of pulsatile index values in the sequential anastomosis with Dg

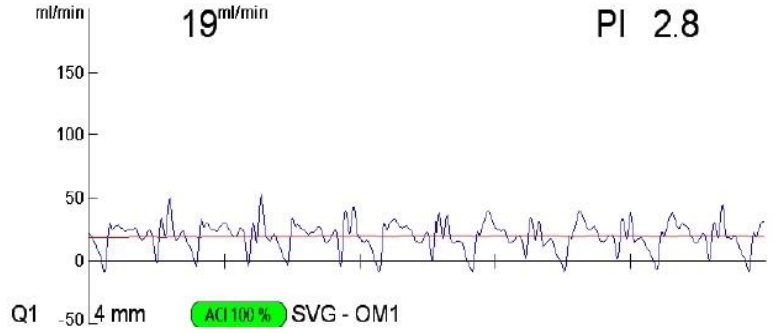

Figure 7. Presence of distal blood flow. A considerable blood flow increase with preservation of pulsatile index values in the sequential anastomosis with OM1

2. In the second patient S.B.S aged 72 years, emergency revascularization of four coronary arteries is accomplished. In this patient, the following diseases are diagnosed: IHD, unstable angina pectoris with crescendo course and three-vessel coronary artery disease along with the following accompanying diseases: diastolic and systolic left ventricular dysfunction, left ventricular heart failure of III NYHA class, arterial hypertension of III degree and of cardiac-cerebral form, hypertensive heart, type 2 diabetes mellitus and peripheral arterial disease of the lower extremities. LIMA is prepared as a free graft because of its poor quality in the proximal area. The left anterior descending coronary artery and its diagonal branch are revascularized with a free LIMA graft as to the diagonal branch, a laterolateral sequential anastomosis is accomplished. The marginal branch of the circumflex artery and the right coronary artery are revascularized with venous grafts. The free LIMA graft is anastomosed proximally to the venous graft originating from the two other coronary arteries. The blood flow in the grafts is measured after aorta declamping and heart function restoration. Through the free LIMA, no blood flow neither to the diagonal

branch, nor to LAD could be encountered at all (Figure 8 and Figure 9). The pulsatile index is high. Good pulsations are palpable in the free LIMA graft. Electrocardiographic and haemodynamic signs of ischemia are lacking. The values of the flowmetric parameters in the venous grafts are optimal.

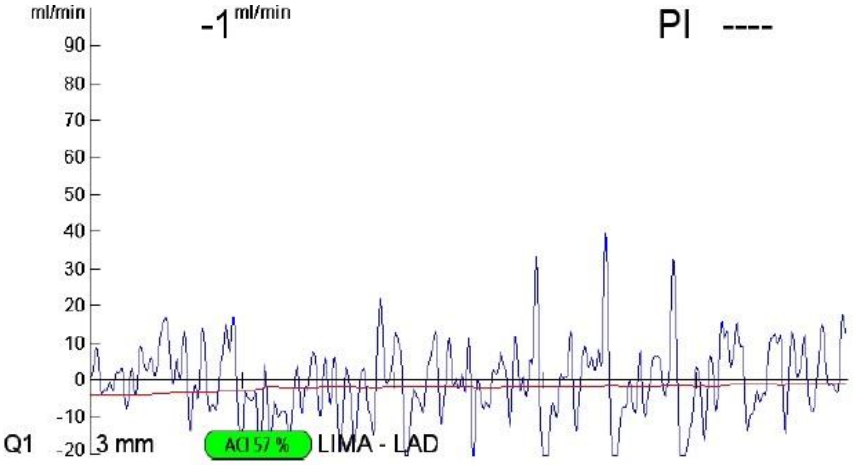

Figure 8. Absent blood flow through LIMA towards LAD

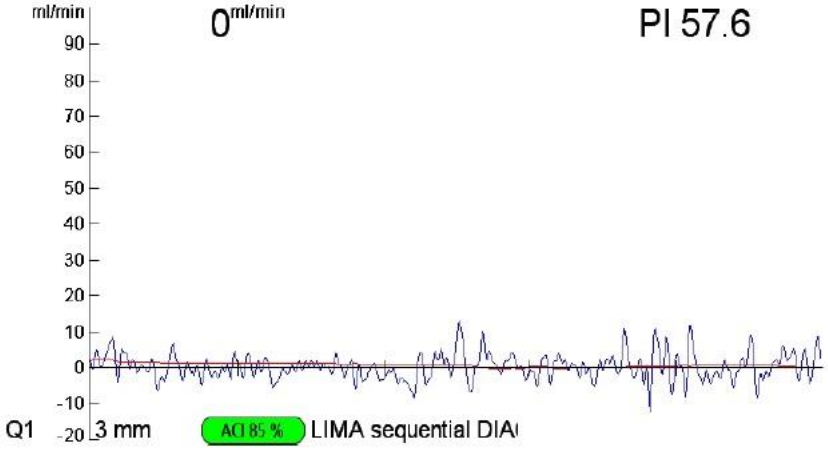

Figure 9. Absent blood flow through LIMA towards Dg

A revision of the anastomoses to the diagonal branch and LAD is needed. A dissecation all along the LIMA necessitates LIMA removed. The sequential anastomoses to LAD and diagonal branch are performed with an additional *v. saphena magna* segment. There are optimal blood flow values through the revised anastomoses after the accomplishment of the proximal anastomosis, aorta declamping, and heart function restoration, even after CPB cessation and heparin effect reversing (Figure 10 and Figure 11). After graft revision, there is a uneventful postoperative period.

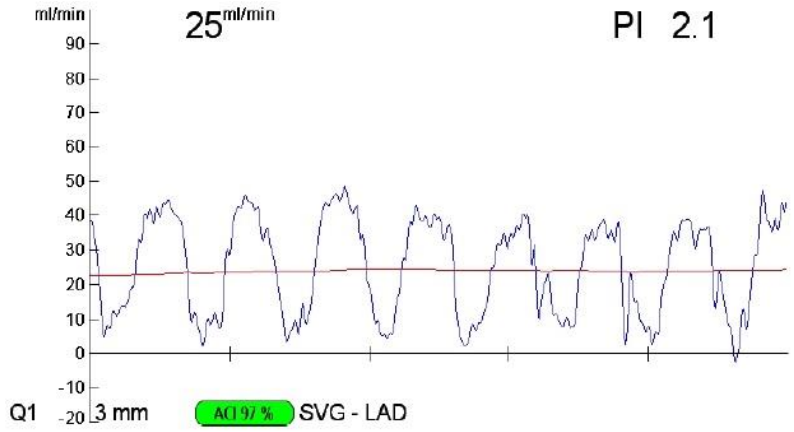

Figure 10. Blood flow towards LAD after graft revision

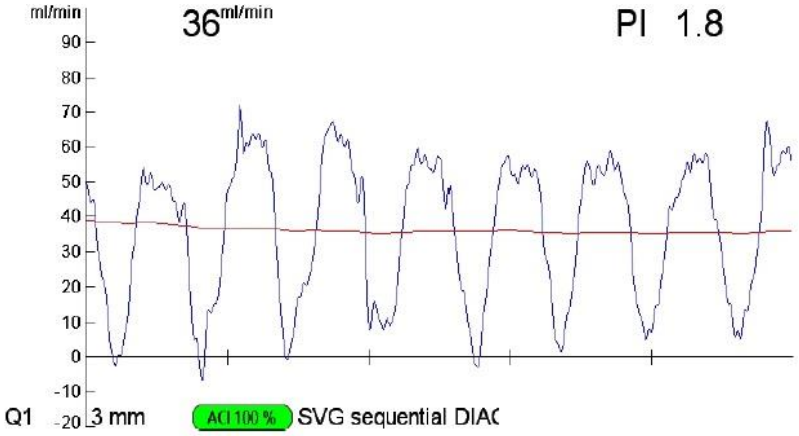

Figure 11. Blood flow towards the diagonal branch after graft revision

4.5. Correlation dependences between the different parameters

The correlation analysis of the results from the comparative investigation of the concrete operative, haemodynamic and laboratory parameters of the patients reveals several statistically significant correlation dependences.

There is a statistically significant inverse correlation between the blood flow values and pulsatile index ones in the arterial grafts within the whole sample of the patients operated on (Pearson coefficient of -0,262; p=0,001) and a borderline statistically significant inverse correlation in on-pump-operation (Pearson coefficient of -0,202; p=0,053).

There is a statistically significant inverse correlation between the number of damaged arteries and blood flow values in the venous grafts within the whole sample of the patients operated on in on-pump-operation only (Pearson coefficient of -0,341; p=0,005).

There is a statistically significant correlation between the number of damaged arteries and pulsatile index values in the venous grafts within the whole sample of the

patients operated on in off-pump-operation only (Pearson coefficient of 0,311; p=0,038).

5. DISCUSSION

5.1. Operative characteristics in conventional CAB and CAB on a 'beating heart'

We performed a total of 235 coronary arterial anastomoses in the patients with CAB on a 'beating heart' and a total of 226 coronary arterial anastomoses in those with conventional CAB. It dealt with 181 arterial and 54 venous conduits in the patients with CAB on a 'beating heart' and with 131 arterial and 95 venous conduits in those with conventional CAB.

The influence of the number of the arterial conduits used in conventional CAB and CAB on a 'beating heart' is analyzed in 5195 patients with a single arterial graft and 1208 patients with multiple arterial conduits for revascularization by means of conventional CAB as well as in 4412 patients with a single arterial graft and 1818 patients with multiple arterial conduits for revascularization by means of CAB on a 'beating heart' (U. Benedetto *et al*., 2017). After a mean follow-up time of 8.2±4.7 years, in the propensity score-weighted sample, survival probabilities at 10 years are 74.5±0.4, 79.7±0.4, 73.4±0.5, and 79.0±0.5. The application of multiple arterial conduits for revascularization by means of CAB on a 'beating heart'and that of multiple arterial conduits for revascularization by means of conventional CAB are associated with a lower late mortality rate as compared with standard single arterial graft for revascularization by means of conventional CAB.

Thirty-one of our patients are revascularized by means of CPB and a single arterial graft or by means of more arterial grafts each; 19 patients are revascularized by means of CAB on a 'beating heart' and a single arterial graft only while 54 patients are done by means of more arterial grafts.

Concerning the operative interventions according to plan, there are no differences in terms of the 30-day mortality rate and postoperative cerebrovascular accidents as well as the necessity of renal replacement therapy.

Among 973 consecutive patients propensity-matched on preoperative characteristics such as age, sex, and risk factors undergoing CAB, a total arterial revascularization technique is compared with a conventional approach (LITA on LAD plus additional *vena saphena* grafts) (G. Bisleri *et al*., 2017). Mean number of grafted vessels (2.39±0.55 versus 2.37±0.7; p=0.79) and aortic cross-clamping time (36±6 versus 35±6 min; p=0.31) are similar while CPB time is significantly longer in a conventional approach (50±7 versus 70±8 min; p=0.03). In-hospital mortality (0.6% versus 1.3%; p=0.41) and overall incidence of postoperative complications are also comparable. Cox regression analysis depicts conventional CAB as an independent predictor for MACCEs (p<0.001). During a median follow-up time of 112 months actuarial survival free from cardiac death (100% versus 95±2.1%; p=0.046) and

MACCEs (97.3±1.5% versus 79.4±3.8%; p<0.001) are significantly improved in patients undergoing total arterial grafting.

In a total of 39 of our patients undergoing total arterial revascularization and routinely used conduits such as LIMA to LAD and venous graft to the rest coronary arteries, there is no statistically significant difference in terms of the number of the anastomoses done (3.07±0.80 versus 3.20±0.86; p=0.698) and the mean aortic cross-clamping time (58.20±16.55 min. versus 66.13±32.48 min.; p=0,210). There is a statistically significantly shorter operation time of CPB in total arterial revascularization than in conventional conduits (89.67±21.96 min. versus 128.93±69 min.; p=0.045). In-hospital lethality rate is 0% versus 12.5%.

Five-year rates of overall death, cardiac-related death, myocardial infarction, repeat revascularization, stroke and new occurrence of postoperative renal failure in a large cohort of patients with coronary disease undergoing isolated surgical coronary revascularization are compared over the period between January 1, 2003 and December 31, 2013 (F. Nicolini *et al*., 2016). There are 6711 patients treated with conventional CAB and 597 ones treated with CAB on a 'beating heart'. The number of bypass grafts is statistically significantly greater in conventional CAB than in CAB on a 'beating heart' (2.4±1.1 versus 1.6±0.9; p<0.0001). Total and cardiac-related mortality rate and the need for repeat revascularization procedures are statistically significantly less in the first than in the second group. The multivariate analysis of significant predictors of mortality in the overall population confirms that the CAB on a 'beating heart' revascularization strategy is an independent predictor of death at long-term follow-up. The conventional CAB reports significantly better results in terms of mortality in the subgroups of patients with a depressed left ventricular ejection fraction and in patients with three-vessel disease. The CAB on a 'beating heart' should be predominantly applied in patients for whom the perioperative risk of CPB is greater than that of a less complete coronary revascularization.

We establish statistically significantly more performed anastomoses in conventional CAB (3.53±0.89) than in CAB on a 'beating heart' (2.97±0.97) (p=0.021). Within our study, there are no patients admitted for repeat revascularization after CAB by means of CPB as well as after CAB on a 'beating heart'.

Within the Arterial Revascularisation Trial, 3102 patients in 28 hospitals in seven countries are randomised to bilateral internal thoracic arteries (n=1548) or single internal thoracic arteries (n=1554) (A. M. Gray *et al*., 2017). Operative time is by 20 min. longer in group one (between 15 min. and 25 min.; p<0.001). These patients require more treatment for sternal wound problems. Mean total costs per patient at 12 months are £13 839±10 534 for bilateral internal thoracic arteries and £12 717±9719) for single internal thoracic arteries. The mean cost difference is £1122 (95% CI £407 to £1838; p=0.002).

We encounter wound complications in the group with CAB by means of CPB in one out of 25 patients when both internal thoracic arteries are applied (in 4%) and in two out of 44 patients after CAB on a 'beating heart' when these arteries are used

(in 4.54% of the cases). There are no wound complications in the patients when a single internal thoracic artery in both operative methods is used.

It should be emphasized that there is no profound infection in these patients. That is why a considerable prolongation of the hospital stay and a raise of therapeutic cost are avoided.

When analyzing a great number of operations with conventional CAB in the USA, Australia and New Zealand, T. A. Schwann *et al.* (2017) establish three multi-arterial coronary artery bypass grafting groups: LITA+RA, BITA, and BITA+RA, each with or without supplemental saphenous vein grafts. The single arterial graft is the most common grafting strategy (in 89.3% in the USA and in 51.4% in Australia and New Zealand). In the USA, between 2004 and 2014, the single arterial graft rates systematically increase from 85.2% to 91.7%, while radial artery use decreases from 10.5% to 3.7%. In the same time, the single arterial graft rates increase from 17.3% to 51.4%, while radial artery grafting decreases from 65.8% to 39.0%.

The overall rate of conversion from CAB on a 'beating heart' to conventional CAB in a sample of a total of 196576 patients undergoing planned CAB on a 'beating heart' within the Society of Thoracic Surgeons National Database from July 2007 to June 2014 is 5.5% (B. Keeling *et al*., 2017). The conversions are planned in 49.6% of the cases. Advanced age, ejection fraction (EF) less than 35%, preoperative intraaortic balloon pump placement, increasing number of corrupted coronary arteries, preoperative heart failure within two weeks, and urgent procedural status are independent predictors for conversion to conventional CAB ($p \leq 0.01$).

Conversion from CAB on a 'beating heart' to conventional CAB from 2001 to 2010 in the Republic of Korea is accomplished in 47 out of 283 IHD patients (in 16.61% of the cases) (S. S. Yoon *et al*., 2017). The major risk factors for this procedure are congestive heart failure ($p=0.029$) and EF less than 35% ($p=0.012$), while preoperative beta-blocker administration can prevent transition to conversion ($p=0.007$). The use of intraoperative ($p=0.007$) and postoperative ($p=0.021$) inotropic support as well as the amount of postoperative drainage ($p<0.001$) and transfusion ($p<0.001$) are statistically significantly higher in the patients undergoing conversion.

Conversion to CPB is necessitated in three out of 79 patients of ours after CAB on a 'beating heart' (in 3,8% of the cases). In two patients, this is accomplished according to plan because of arrythmias during surgery. In these patients, EF is greater than 35%.

In one patient with preoperative EF of 35%, the emergent conversion is accomplished on the background of haemodynamic instability. He necessitates infusion of inotropic means and implantation of an intraaortic balloon pump while in the patients with planned conversion, such a postoperative inotropic support is not needed. No considerable mediastinal bleeding during the postoperative period has been observed and there is no need of blood transfusion during the reanimation period.

The influence of surgical revascularization on different timing after ST-elevation myocardial infarction (STEMI) on 225 patients, 186 males and 39 females, admitted from January 2003 to July 2012 with coronary artery disease and left

ventricular dysfunction (EF <50%) is investigated (R. Wang *et al*., 2014). The patients are divided into three groups - with early revascularization (<21 days - 20 males and 9 females at mean age of 63±10 years), with mid-term revascularization (after 21 to 90 days - 48 males and 16 females at mean age of 63±8 years), and with late revascularization (>90 days - 118 males and 14 females at mean age of 62±10 years). Thirty-day post-operative mortality rates are 3.4%, 0 and 2.3% among three groups, respectively. The difference is not statistically significant (χ^2=2.137; p=0.330). Low cardiac output syndrome mortality rates are 13.8%, 3.1% and 2.3% as the difference between three groups is statistically significant (χ^2=8.344; p=0.015). Left ventricular EFs are improved in all the three groups. Their preoperative values are 42%±6%, 41%±6% and 42%±6%, while their postoperative values are 46%±7%, 45%±10% and 45%±9%, respectively (*t*=-3.378 to -2.339; all p<0.05). The left ventricular end diastolic dimensions are statistically significantly reduced in the mid-term and late revascularization groups only from 54±6 mm and 55±6 mm before to 47±8 mm and 49±9 mm after surgery (*t*=5.634 to 5.885; p=0.001).

A total of 10 patients of ours undergo revascularization after STEMI. In both groups, there are five patients, three males and two females each representing 6,3% in the CAB on a 'beating heart' group and 7,8% in the CAB with CPB one. All the patients in group one are revascularized within <21 days after the acute accident. Four patients in the second group are revascularized within <21 days and one patient is done within >21 days after the acute accident. The values of EF do not differ statistically significantly between both groups: 40.6±4.98 versus 40.2±9.36, respectively. Only one patient in the second group deceases during the perioperative period. Thirty-day lethality rate is 0% in both groups.

The retrospective analysis of 780 patients undergoing CAB on a 'beating heart' divided into three groups (262 aged <65 years, 329 aged 65-74 years and 189 aged >75 years) demonstrates similar in-hospital mortality rates of 0.8%, 1.2% and 1.1%; p=0.862), respectively (S. Ohira *et al.*, 2015). According to multivariate Cox models, the NYHA classification (p=0.009) and left ventricular EF (p=0.016), but not patient's age are independent risk factors predicting cardiac events.

M. F. Ismail *et al*. (2017) juxtapose the influence of some factors on the occurrence of postoperative atrial fibrillation in 84 out of a total 252 patients at a mean age of 65 years undergoing conventional CAB. These patients have a lower left ventricular EF (44.8±5.7%; p=0.0001), diastolic dysfunction (p =0.0001), and a larger left atrial volume (p=0.0001). Bleeding requiring a repeated exploratory opening of the chest and postoperative shock represent significant predictors of postoperative atrial fibrillation.

We register a postoperative atrial fibrillation in 16 patients (in 20,2%) with CAB on a 'beating heart' and in nine ones (in 16,4% of the cases) with conventional CAB. This difference is statistically significant (p=0.007). In both groups, there is no relationship between EF values and atrial fibrillation occurrence.

From January 2003 to July 2013, 318 patients, 266 males and 52 females aged 36 to 83 years (63±9) with IHD and left ventricular EF ≤50% are examined (R. Wang

et al., 2016). CAB on a 'beating heart' is accomplished in 76 patients and conventional CAB is done in 242 ones. Operative mortality rate is 1.89% (six deaths). With follow-up time from one to 128 months, there are 287 cases causing a follow-up rate of 92.25%. All-cause death and cardiogenic death amount to 42 patients (14.63%) and 17 patients (5.92%). Re-hospitalization occurs in a total of 42 patients (in 14.63% of the cases). Re-revascularization rate, recurrent angina pectoris rate and cerebral accident incidence are 3.48% (10 patients), 13.59% (39 patients) and 1.74 % (five patients), respectively. The five-year survival rate is 85.6%. With all-cause death as the endpoint, preoperative left ventricular EF (p=0.031) and perioperative implantation of an intraaortic balloon pump (p=0.038) emerge as the main risk factors that affect the long-term survival. The five-year survival rate of the patients with severe left ventricular dysfuntion (left ventricular EF≤35%) is statistically significantly lower than that of patients with mild to moderate left ventricular dysfuntion (35%<left ventricular EF≤50%) (70.4% versus 86.1%; p=0.025).

The operative lethality rate in our patients is 2.8% (four deaths). A total of 33 patients (23.07% of the cases) are followed-up for six to 23 months after the operative intervention. Three patients (2.1% of the cases) are rehospitalized in the Clinic of Cardiology during this period because of cardiac insufficiency manifestations. There are no data about any postoperative angina pectoris symptoms and ischemic brain accidents at all.

According to ANOVA results, there are statistically significant differences between the different number of the grafts used concerning the mean duration of off-pump-operation (F=16.180; p=0.0001).

From July 1997 to December 2012, D. Samim *et al*. (2015) perform conventional CAB in 124 consecutive patients and CAB on a 'beating heart' in 119 ones for isolated revascularisation of the anterior descending coronary artery. In the first group, aortic cross-clamping and CPB times are 22 and 35 min., respectively. Mean surgical time is 160 min. for the conventional CAB and 126 min. for the CAB on a 'beating heart' as this difference is statistically significant (p<0.001). Statistically significantly less emergency procedures are performed in CAB on a 'beating heart' than in conventional CAB (3.4% versus 11%; p=0.042). Besides in the first group, there are more men than women (82% versus 66%; p=0.006), older patients (at a mean age of 67 versus 64 years; p=0.013), patients with renal failure (11% versus 2.4%; p=0.009) and respiratory failure (20% versus 7.3%; p=0.003), patients with peripheral vascular disease (PAD) (17% versus 8%; p=0.038) as well as with higher degree of angina pectoris (p<0.001).

The operative times of the surgical interventions in our patients are 267.02±54.5 min. on the average in the group with CAB on a 'beating heart' and 322.45±78.5 min. in that with CAB with CPB. This difference is statistically significant (p=0.001). Emergency surgery is performed statistically significantly less common in the first than in the second group (2.5% versus 18.7%; p=0.001). Males prevail statistically significantly in the first group (83.5% versus 70.3%; p<0,001).

The incidence rate of accompanying chronic PAD is statistically significantly smaller in the first than in the second group (7.6% versus 17.1%; p=0.024).

The retrospective analysis of 25 patients undergoing minimally invasive CAB on a 'beating heart' via a single left thoracotomy for revascularization with bilateral internal thoracic arteries and of 37 patients with a single internal thoracic artery demonstrates only one lethal case in the second group (K. Kikuchi *et al*., 2017). The mean duration of the operation is longer in the first than in the second group (265±104 min. versus 336±73 min.). There are no major postoperative complications in the first group. Computed tomography (CT) angiography proves that all the grafts in this group are patent one week following the operation.

Since spring of 2017, we have initiated the minimally invasive direct CAB for LAD revascularization by using the left anterior thoracic artery as arterial graft. During the present study, a total of five patients with CAB on a 'beating heart' (6.3% of the cases) are revascularized by this minimally invasive method. The mean duration of the intervention is 196±81.5 min. There are no significant postoperative complications. The blood flow and pulsatile index present with optimal values at the end of the intervention.

During the period between 2000 and 2007, J. Karhunen *et al*. (2010) perform CAB in 5251 patients at a mean age of 64.0 years and early coronary angiography for postoperative persistent myocardial ischaemia in 23 of them (in 0.44% of the cases). A reoperation is carried out in five of these 23 patients (in 21.74% of the cases). Intensive coronary unit stay is 5.72±0.98 days and hospital stay is 12.2±1.54 days. Myocardial infarction rate in all the patients is 63.8% and in-hospital mortality rate is 22.2%.

The application of univariate analysis identifies the relationship between diabetes mellitus, on the one hand, and longer intensive coronary unit stay (55.2±53.0 hours versus 49.29±51.30 hours; $p<0.05$), postoperative new-onset atrial fibrillation (20.9% versus 14.97%; $p<0.05$) and postoperative infection incidence rate (9.2% versus 4.67%; $p<0.05$), on the other hand, in the patients undergoing CAB on a 'beating heart' (Y. Liu *et al*., 2016).

There exists a undoubted relationship between diabetes mellitus and postoperative wound infection. In our practice, we approve some rules which observation considerably reduces the risk of wound infection in the patients, particularly in those of them who undergo bilateral internal thoracic artery preparation. One bears in mind thoracic artery skeletonization, ultrasound scalpel utilization and preservation of sternal venous drainage.

A superficial wound infection is postoperatively diagnosed in three of our patients (in 2.09% of the cases). In one patient presenting with CAB with CPB and two patients doing with CAB on a 'beating heart', both thoracic arteries are used as conduits. In these three patients, there is accompanying type 2 diabetes mellitus. No wound complications during the application of the single internal thoracic artery in both patient's groups are observed at all.

The early results in a total of 300 patients with coronary artery disease undergoing CAB on a 'beating heart' or conventional CAB in Pakistan are

retrospectively analyzed (G. Hussain *et al*., 2016). The CK-MB concentrations, need and duration of inotropic support, mechanical ventilation time and intensive coronary unit stay are statistically significantly less in the patients after CAB on a 'beating heart' ($p=0.001$; $p<0.0001$; $p=0.006$; $p=0.025$ and $p=0.001$), respectively. The perioperative chest drainage is statistically significantly higher in the patients after the conventional CAB ($p=0.027$).

In our patients, postoperative inotropic support is statistically significantly less commonly needed in the group with CAB on a 'beating heart' (in 13.9%) than in the group in CAB with CPB (in 41.8% of the cases) ($p<0.001$). There is no considerable difference in terms of the time (in hours) for mechanical ventilation between both groups (9.4±4.2 in the first versus 10.0±5.8 in the second group; $p=0.176$).

We establish a considerable comorbidity in our IHD patients. It undoubtedly exerts unfavourable influence upon the operative outcomes, however, it is not an object of the present investigation.

D. Pevni *et al.* (2017) juxtapose the outcome in 535 consecutive patients undergoing CAB on a 'beating heart' with grafts from bilateral internal thoracic arteries with that in 422 consecutive patients undergoing this procedure with a single internal thoracic artery from saphenous vein or radial artery grafts during the period between 2000 and 2008. The incidence rate of the following parameters is less in the first than in the second group: being female (20.9% versus 36.0%; $p<0.001$), having diabetes mellitus (36.6% versus 55.7%; $p>0.001$), recent myocardial infarction (23.6% versus 33.2%; $p>0.001$), age ≥70 years (41.1% versus 49.8%; $p=0.001$), PAD (26.1% versus 46.7%; $p>0.001$), and chronic renal failure (7.9% versus 15.9%; $p>0.001$). The European System for Cardiac Operative Risk Evaluation score is statistically significantly higher in the second group (7.62 versus 5.46; $p=0.001$), whereas operative mortality rate (2.6% versus 1.7%) and sternal wound infections (2.1% versus 1.7%) are similar in both groups. During the mean follow-up of 11.6±3.5 years, patients' ten-year survival rate is statistically significantly better in the first than in the second group (72.2% versus 55.1%; $p>0.001$).

Myocardial revascularization with bilateral internal thoracic arteries undoubtedly leads to excellent results in terms of long-lasting graft patency and corresponding long-term survival. In our practice, we pay special attention to female patients, patients with BMI >32 as well as with diabetes mellitus and its complications. In them, the risk of development of deep wound infections is mainly discussed as they could corrupt the expected outcomes from the usage of two arterial grafts.

When glycated haemoglobin level (HbA1c) values are <7%, i.e. in case of a good control of the disease, we perform myocardial revascularization by means of both internal thoracic arteries. The values of HbA1c >7% represent an indication for a standard revascularization strategy of applying the left internal thoracic artery and a venous graft. When subclavian artery stenoses are lacking, peripheral arterial insufficiency represents an indication for the application of the bilateral internal thoracic arteries in our practice as the wound infections in the area of prepared saphenous-vein conduits are not any rarity in such patients and are due

predominantly to the disturbed trophics of lower extremity tissues. Of course, in the patients with risk factors, it is of utmost importance to minimize electrocauterization usage as we apply a method of skeletonization by means of ultrasound scalpel and venous drainage preservation along the thoracic arteries. According to our modest opinion, when applying this method there are no deep wound infections and the number of the superficial ones is minimized.

5.2. Clinical application of intraoperative transit-time flowmetry in conventional coronary artery bypass and coronary artery bypass on a 'beating heart'

The comparison of the mean pulsatile index values in the arterial grafts in on-pump- and off-pump-operations by means of independent samples *t*-test reveals a statistically significant difference between these two operative methods (p=0.003).

There is a statistically significant inverse correlation between the blood flow values and pulsatile index ones in the arterial grafts in all the patients operated on (Pearson correlation coefficient of -0.262; p=0.001) as well as a borderline statistically significant inverse correlation in on-pump-operation (Pearson correlation coefficient of -0.202; p=0.053).

A statistically significant inverse correlation between the number of the corrupted coronary arteries and blood flow in the venous grafts within the whole sample of our patients (Pearson correlation coefficient of -0.341; p=0.005) is observed.

A statistically significant correlation between the number of the corrupted coronary arteries and pulsatile index in the venous grafts within the whole sample of our patients during the off-pump-operation only (Pearson correlation coefficient of 0.311; p=0.038) is observed.

In 2010, conventional CAB is performed in ten while CAB on a 'beating heart' is done in 25 patients in the city of Salvador, Brazil (F. M. Cerqueira Neto *et al*., 2012). The mean number of the anastomoses accomplished is 2.2±0.6 and 2.3±0.8 (p=0.10), the mean blood flow is 23 mL/min. and 25 mL/min. (p=0.34), the pulsatile index is 2.3 и 2.2 (p=0.82), while the diastolic filling percentage is 56% and 56.9% (p=0.86), respectively. The flowmetric parameters concern the blood flow through LIMA to LAD only.

The mean number of the anastomoses with CAB on a 'beating heart' is 2.97±0.96 and of those with CAB with CPB is 3.53±0.89 as this difference is statistically significant (p=0.014). The mean values of the blood flow measured in the internal thoracic artery is smaller in the first than in the second group (28.07±14.30 mL/min. versus 40.25±28.22 mL/min.; p=0.003). The mean values of the pulsatile index in the first group are 3.34±0.96 and in the second one are 2.70±2.14, however, this difference is statistically insignificant (p=0.057).

A case-control retrospective study of 65 saphenous vein grafts from 44 patients from Graft Imaging to Improve Patency, a single-center, randomized blinded clinical trial is carried out (D. Une *et al*., 2013). Twenty-two saphenous vein grafts are

occluded. The tranit-time flowmentric mean blood flow is statistically significantly predictive of one-year saphenous vein graft failure ($p<0.01$), while according to logistic regression models - of early graft failure, too ($p=0.014$). Its cut-off value of 31 mL/min. is of statistically significant ($p=0.017$) sensitivity of 63.6% and specificity of 67.4%. The risk of graft occlusion is 50% for grafts with mean blood flow <31 mL/min and 21.6% for grafts with mean blood flow ≥31 mL/min..

The control CT angiography in 33 patients of ours at least six months following surgery identifies four corrupted venous grafts. In these grafts, the mean blood flow and pulsatile index are 13.50±8.96 mL/min. and 4.65±2.74, respectively, while in 25 not occluded grafts, these values are 32.70±17.14 mL/min. and 2.43±1.26, respectively.

We consider the values of the blood flow <15 mL/min. and the pulsatile index >4.0 as threshold for the mid-term venous graft patency. The type of operative intervention should additionaly be taken into consideration as in CAB on a 'beating heart', there are three occluded venous grafts while in CAB with CPB, there is only one occluded venous graft since the number of control CT angiographies (17 versus 16) as well as the number of the venous anastomoses (14 versus 15) done in the patients with this imaging examination are approximately equal.

A total of 1394 grafts in 436 consecutive patients undergoing CAB (3.2 grafts per patient) are intraoperatively assessed by transit-time flowmetry in Jordan (B. Harahsheh, 2012). Inadequate flowmetrtic values are established in 100 grafts (in 7.17% of the cases). They are most common in the circumflex and right coronary artery systems (in 9.4%) and the least in the left anterior descending artery system (in 4.4% of the cases). The mean blood flow of grafts to the left anterior descending artery is 33.4±5.3 mL/min with a pulsatile index of 2.4±0.4. The corresponding values of the grafts to the circumflex and right coronary artery are the following: mean blood flow of 35.1±7.2 mL/min. with a pulsatile index of 3.5±0.7 and mean blood flow of 38.4±5.9 mL/min. with a pulsatile index of 2.6±0.6. Revisions occurs in five patients (in 1,15% of the cases).

We encounter unacceptable flowmetric parameters in 16 out of 461 grafts (in 3.47% of the cases) and perform, therefore, revision. There are nine revisions (56.25%) in the area of LAD and seven ones (43.75% of the cases) in the area of the right coronary artery and circumflex artery. The mean blood flow to LAD is 32.7±22.5 mL/min. and the mean pulsatile index is 3.1±1.6. The mean blood flow values in the grafts from the circumflex and the right coronary artery are 27.5±17.5 mL/min. and the mean pulsatile index value is 2.8±1.6.

In a prospective randomized study from October 17, 2006, to July 30, 2009, a total of 888 patients undergoing mainly isolated CAB on a 'beating heart' and a total arterial revascularization in Y and T configuration in Poland are analyzed (P. Zelazny *et al*., 2010). Transit-time flowmetry measurements are performed in 305 patients only. In 28 of these patients (in 9,18% of the cases), blood flow measurements of 29 anastomoses show unacceptable results of checked parameters. After graft revision, they are completely corrected.

These results support the diagnostic role of the flowmetric examination in coronary artery surgery. The method is easy to perform and, in our opinion, its routine application in practice could lead to still better outcomes.

In 47 of our patients (in 32.7% of the cases), we make use of the bilateral internal thoracic arteries to the purposes of the total arterial revascularization, and in two cases - of the radial artery of the non-dominant arm as an additional graft. The composite graft between both internal thoracic arteries is constructed through 'Y'- or 'T'-anastomosis. The flowmetric examinations demonstrate abnormal blood flow values (<10 mL/min.) in two out of a total of 128 distal anastomoses (in 1.6% of the cases) while pulsatile index values are <3. That is why no revision of these anastomoses has been undertaken.

Transit-time flow measurements are done in the first 1000 CAB operations performed in the Cardiovascular Clinic, University Clinical Centre Tuzla, Bosnia and Herzegovina, between September, 1998 and September, 2003 (E. Mujanović *et al*., 2007). It deals with 1394 grafts in CAB on a 'beating heart' group and 1478 grafts in conventional CAB group. In group one, 38 grafts (2,72%) in 37 patients (7,07%) while in group two, 26 grafts (1,75%) in 26 patients (5,45%) are revised. However, this difference is statistically insignificant (p=0,1035). One patient in group one needs two graft revisions. Most frequently, grafts to LAD are revised.

We revise four out of a total of 235 anastomoses in CAB on a 'beating heart' (in 1.7%) in four out of 79 patients (in 5.1% of the cases). We revise 13 out of a total of 226 grafts (in 5.6%) in CAB with CPB in 10 out of a total of 64 patients (in 15.6% of the cases). Analogous results are reported by E. Mujanović *et al.* (2007), the revision of the LAD is most common in our patients, too.

Routine measurements of 167 *vena saphena* grafts to the left and 134 grafts to the right cardiac area are accomplished by means of transit-time flowmetry in 207 patients undergoing CAB (S. Amin *et al*., 2018). There are no statistically significant differences between both cardiac areas in terms of the mean values of blood flow and pulsatile index. There is a statistically significantly greater percentage of diastolic filling in left-side *vena saphena* grafts within the whole sample (p<0.001), in conventional CAB (p<0.001) and in CAB on a 'beating heart' (p=0.07), as well as a greater percentage of recurrent blood flow in these left-side grafts in CAB on a 'beating heart' (p=0.023). The results from the multivariation regression analysis demonstrate a strong association between this anastomosis and the greater percentage of diastolic filling (p<0.001).

We establish statistically significantly different mean blood flow values between the left and right coronary arteries within our whole sample in 71 venous grafts to the branches of the left and in 60 grafts of the right coronary arteries (p=0.024). These values are higher to the right coronary arteries. There is no statistically significant difference concerning the corresponding values of the pulsatile index (p=0.331). Diastolic blood flow volume is completely logically greater in the grafts to the left coronary arteries. This fact is related to the anatomical peculiarities of the left ventricle which possesses a more outlined muscle tissue. This determines the passage of a greater blood amount through the coronary arteries

during diastole. As the right ventricle presents with thinner walls, the blood flow through the right coronary artery can be equal during the systole and diastole as well.

Flowmetric and angiographic assessments of 235 autoarterial and 117 autovenous bypass grafts are performed in 141 patients undergoing CAB (V. V. Bazylev *et al.*, 2018). During the follow-up period of up to 42 months, there are 33 (14.04%) occluded arterial conduits and 30 (25.64%) venous ones. During this period, the probability of the lack of occlusions of venous grafts amounts to 74.4±5.8% and that of arterial grafts is 86±3.3%, i. e. during the follow-up period of up to 42 months, the probability of occlusion of venous grafts is statistically reliably much higher than that of arterial ones (log rank=0.006). Graft occlusion is influenced by the increased peripheral resistance index (p=0.033), the decreased volumetric blood flow velocity in the graft (p=0.005, and the type of the venous graft (p=0.001).

We perform CT angiographic examination in 78 arterial grafts and 22 venous ones. During the follow-up for at least 23 months, we establish eight occluded arterial grafts (10.26%) and four occluded venous ones (18.8% of the cases). The probability of the absent occlusion of arterial grafts in our patients is 89.74% but that of the arterial ones is 81.81%. Similarly to the study of V. V. Bazylev *et al.* (2018), the probability of occlusion of grafts at the end of the first year of the follow-up is greater when the venous grafts are concerned. We establish only six occluded arterial conduits along with acceptable blood flow data (>15 mL/min.) and pulsatile index ones (<5). In two of these six arteries, the blood flow is 46 mL/min. and 44 mL/min., respectively, while the pulsatile index is 2.3 and 1.3, respectively. In our opinion, the flowmetric parameters can influence upon graft patency in two arteries only. These parameters can be related to the result from the CT angiography examination in one out of the four occluded venous grafts only. We accept that their prognostic value in our patients is limited.

A total of 1240 patients (856 males and 384 females at a mean age 57.4±12.1 years; range, 47 to 74 years) undergoing isolated CAB via median sternotomy are retrospectively analyzed through transit-time flow measurement during the perioperative period (U. Kaya *et al.*, 2018). In 146 grafts of 143 patients with insufficient patency, anastomosis/graft revision, new anastomosis/patch plasty to distal native artery, or free left internal thoracic artery graft are performed. The coronary blood flow in four grafts with insufficient flowmetric parameters is corrected by extending the short length of the graft.

By means of transit-time flowmetry we establish an insufficient patency in 16 out of a total of 461 grafts of 13 out of a total of 143 patients. In 15 grafts, the revision consists in performance of a new anastomosis and subsequent correction of the flowmetric parameters. In one patient, these insufficient parameters are corrected by using graft shortening.

Postoperative coronary angiography within one month after isolated CAB is performed from 2009 to 2015 in 196 out of 491 patients with chronic total occlusion in Japan (H. Oshima *et al.*, 2016). A total of 214 conduits (103 arterial and 112 of *vena saphena*) are anastomosed to the vessels with chronic total occlusion and undergo intraoperative transit-time flowmetry measurements. There are 78 grafts

from left internal thoracic artery, 10 ones to the right internal thoracic artery and 14 ones from the right gastroepiploic artery. The transit-time flowmetry variables recorded early in failing grafts after CAB in the patients with chronic total occlusion have a lower mean flow and a higher pulsatile index when compared with patent grafts. These values are namely useful to detect early graft failure in conduits anastomosed to vessels with chronic total occlusion. There is no association between Rentrop collateral grade and graft failure. However, CAB usage to such vessels with akinetic/dyskinetic wall motion should be carefully considered.

In our patients, a total of 54 conduits are anastomosed to completely occluded coronary arteries. There are 29 arterial and 25 venous conduits which are intraoperatively assessed by transit-time flowmetry. A total of 18 left internal thoracic arteries, 10 right internal thoracic arteries and one radial artery are used as arterial conduits. Only in two arterial grafts, considerably lower flowmetric values than those of patent grafts are measured that necessitates revision of the anastomosis. Concerning the other venous and arterial conduits which are anastomosed to completely occluded coronary arteries, there is no any difference in terms of the measured values of the blood flow and pulsatile index versus the conduits which are anastomosed to the coronary arteries without any total occlusion at all (of 27.94±17.27 mL/min. in the coronary arteries with total occlusion towards 27.37±14.04 mL/min. in the coronary arteries without any total occlusion at all; p=0.835 and 2.67±1.23 versus 2.54±0.95; p=0.526), respectively.

G. Di Giammarco *et al*. (2017) share their experience with the application of transit-time flowmetry in combination with high-resolution epicardial coronary ultrasonography for intraoperative blood flow evaluation in the coronary grafts. A two-dimensional ultrasound imaging (either in short-axis or long-axis) and colour-flow mapping can be provided allowing an accurate morphological evaluation of body graft and anastomosis. Acording to L. B. Ohmes *et al*. (2017), too, the combination of transit-time flowmetry with high-resolution epicardial coronary ultrasonography is of high diagnostic value in the evaluation of coronary graft blood flow. The fluorescence imaging offers an excellent visualization of the coronary vessels and grafts, however, the publications on this topic are scanty.

Our experience with the application of epicardial coronary ultrasonography in combination with transit-time flowmetry is limited. Several cases when we succeed to supplement the intraoperative transit-time flowmetry with epicardial coronary ultrasonography enable us to accept that the combination of these two methods present with an extraordinarily high diagnostic value for the coronary blood flow evaluation and could eliminate the unnecessary anastomosis revision.

The relationship between preoperative severity of coronary vascular stenosis occurring with different fractional flow reserve and the intraoperative blood flow pattern is retrospectively evaluated in 72 patients in Japan (K. Honda *et al.,* 2015). The patients are divided into three groups according to the following preoperative fractional flow reserve values: of <0.70, between 0.70 and 0.75, and ≥0.75. The mean blood flow values in these groups are the following: 24.7±10.6 mL/min., 19.2±14.0 mL/min. and 16.0±9.7 mL/min., the pulsatile index ones are 2.35±0.6, 3.02±1.1 and

5.51±8.20, while the number of the patients with a systolic blood flow reserve - 3 (6.8%), 5 (35.7%) and 4 (28.6%), respectively. There are statistically significant differences between these three groups in terms of graft blood flow (p=0.009), pulsatile index (p=0.038) and proportion of the systolic blood flow reserve (p=0.023). Graft patency is confirmed with intraoperative fluorescence imaging in all the patients but postoperatively within a time interval of 213 days with multislice CT or coronary angiography in 69 patients.

The preoperative data of the coronary fractional flow reserve could additionally contribute to the quality of the operative treatment in IHD patients. Sometimes, the significant coronary artery sclerosis dispays values of the fractional coronary flow reserve >0.75, whereas transit-time flowmetry proves a reduced blood flow in the graft and increased pulsatile index. When data about the fractional coronary flow reserve in the patients suitable for operative revascularization are not available and flowmetric data are contradictory, the technical problem with the anastomosis, the poor quality of the distal coronary vessel and the presence of the competitive blood flow as conditions which could determine patency prognosis of the corresponding graft should be identified. In these circumstances, the presence of the competitive blood flow can be confirmed through revision of the accomplished anastomosis. The absence of corrected flowmetric values is, more probably, due to the competitive blood flow rather than the technical trouble during anastomosis accomplishment.

Revascularization of left coronary system with composite graft between the left internal thoracic artery and a saphenous vein graft is performed in 23 patients and blood flow is evaluated by transit-time flowmetry in all the graft segments (H. G. Lobo Filho *et al*., 2016). Measures are performed at baseline and after dobutamine-induced stress, without and with non-traumatic temporary clamping of the distal segments of the composite graft. Stress results in a statistically significant increase of blood flow values ($p<0.05$). Non-traumatic clamping of arterial and venous graft segments does not result in statistically significant blood flow changes.

There are no differences between both types of composite grafts concerning blood flow parameters. It is noteworthy that a similar comparison is not appropriate in our practice because of the small number of the patients revascularized with a composite graft of the left internal thoracic artery and venous graft. It deals with two patients with CAB on a ‘beating heart’ against 44 patients in the same group with a composite graft of both internal thoracic arteries. We do not apply the stress-test to prove blood flow augmentation.

In 345 CAB patients, a total of 982 coronary anastomoses are intraoperatively assessed by means of transit-time flowmetry (P. Lehnert *et al*., 2015). Signs of graft failure at one year after surgery are diagnosed by means of coronary angiography in 12% of the cases. Graft failure odds ratios decrease statistically significantly by 4% for every 1 mL/min blood flow increase in internal thoracic artery grafts (p=0.005) and by 2% - in single-vein grafts (p=0.059).

Between March 2007 and February 2008, a total of 121 patients undergo CAB on a ‘beating heart’ and are examined by means of transit-time flowmetry (J. S. Jung

et al., 2012). In 70 patients, there is left internal thoracic artery-left anterior descending and proximal aorta-saphenous vein sequential grafting while in 51 patients, a composite graft between left internal thoracic artery and radial artery sequential grafting. The mean blood flow and pulsatile index of the proximal saphenous vein sequential graft and that of the radial artery graft are 64.4±37.3 mL/min and 2.6±1.6 versus 27.3±18.6 mL/min and 4.1±4.4, respectively ($p<0.05$). In group one, the mean left internal thoracic artery blood flow, pulsatile index, and back flow are 26.9±16.4 mL/min, 2.6±1.5 and 3.1±6.1%. In group two, in the proximal towards the distal left internal thoracic artery, these values are the following: 37.3±21.6 mL/min, 2.3±1.0 and 2.0±3.5% and 18.8±12.2 mL/min, 3.9±3.3 and 7.4±11.8%, respectively ($p<0.01$). The haemodynamic blood flow characteristics of composite bypass grafting are inferior to the single left internal thoracic artery and separate aorta-saphenous vein bypass grafting.

We compare the usage of the venous graft with a proximal sequential anastomosis to the coronary artery and the proximal anastomosis to the aorta as well as of the composite graft from the left and right internal thoracic arteries as the right one has a sequential anastomosis to a coronary artery in 79 patients undergoing CAB on a 'beating heart'. In six patients, there is anastomosis between the left internal thoracic artery and venous graft to the ascending aorta with accomplished proximal sequential anastomosis to the coronary artery whereas in 34 patients, there is a composite graft between the left and right internal thoracic arteries with a sequential anastomosis to a coronary artery. The mean blood flow and pulsatile index values of the proximal saphenous vein sequential graft and those of the right internal thoracic artery are 24.33±17.18 mL/min. and 2.85±0.7 versus 29.33±13.56 mL/min. and 2.68±0.69, respectively ($p>0.05$). In group one patients, the mean blood flow and mean pulsatile index in the left internal thoracic artery are 19±9.5 mL/min and 3,77±0,9, respectively. In group two patients, the mean blood flow and mean pulsatile index in the proximal versus distal left internal thoracic artery are 76.73±37.39 mL/min. and 1.98±0.62 versus 29.38±10.99 mL/min. and 3.34±0.9, respectively ($p<0,05$). In our patients, the composite grafts present with a more favourable blood flow than the single grafts.

Myocardial revascularization without CPB is accomplished in 50 patients divided into two groups (R. Milani *et al*., 2014). Group-one patients at a mean age of 60.6±9.49 years and a mean weight of 80.4±10.32 kg receive graft of right internal thoracic artery to the anterior interventricular branch while group-two patients at a mean age of 59.8±9.7 years and a mean weight of 77.7±14.22 kg receive graft of left internal thoracic artery to the same branch. The average number of grafts per patient in group one is 3.28±1.49 and in group two it is 3.08±0.82. At the end of surgery, mean blood flow is 42.1±23.4 mL/min. and 34.2±19.1 mL/min. and the mean distal resistance is 2.8±0.9 and 2.0±0.7, respectively.

There are interesting results comparing the blood flow to the left anterior descencent coronary artery when using the left and right internal thoracic arteries as arterial conduits. In order to explain the better blood flow through the left internal thoracic artery, one has to examine and juxtapose the free blood flow through both

thoracic arteries and the area of the left anterior descencent coronary artery where the anastomosis has been accomplished, i. e., proximal, middle, or distal third. The right internal thoracic artery is used as a conduit to the left anterior descencent coronary artery in one of our patients only. We avoid this combination consisting of an arterial conduit and target coronary artery because of the fact that the right internal thoracic artery should cross the midline in order to reach the left anterior descencent coronary artery. This increases the risk of damage to the patent arterial conduit in case of necessary resternotomy.

From October 9, 2009 to April 30, 2012, a total of 259 patients undergo robotic-assisted CAB procedures at a univwrsity hospital in Atlanta, the USA (P. F. Walker *et al*., 2013). Of these, 160 patients have both transit-time flowmetry and either intraoperative, or postoperative angiography of the left internal thoracic artery to the left anterior descending coronary artery graft. There are 152 (95%) angiographically perfect grafts. Five grafts are occluded and three have significant flow-limiting lesions. Two patients have intraoperative graft revision after angiography, one has redo CAB during the same hospitalization, and five undergo percutaneous intervention. A statistically significant difference between patent and nonpatent grafts is seen concerning the mean blood flow (34.3±16.8mL/min versus 23.9±12.5 mL/min; p=0.033) but not concerning the pulsatile index (1.98±0.76 versus 1.65±0.48; p=0.16) and diastolic fraction (73.5%±8.45% versus 70.9%±6.15%; p=0.13).

The implementation of the coronary angiography is a golden standard for the evaluation of anastomotic patency after the operative myocardial revascularization. Routine intraoperative application of this method requires, however, a material equipment provided with a hybrid hall and additional staff. In our Clinic, we would perform a coronarographic examination during the early postoperative period in the patients with a clinically manifested ischemia. Taking into consideration even the possible presence of falsely-satisfactory results amounting according to P. F. Walker *et al*. (2013) to 5% of 160 patients, the application of transit-time flowmetry is an easy and rapid method for anastomotic blood flow assessment. The mean blood flow and pulsatile index values in our 139 left anterior descendent artery grafts are 32.720±22.522 mL/min. and 3.050±1.587, respectively. In eight of these arterial grafts, inacceptable results are interpreted that necessitates revision and repeated accomplishment of the anastomosis with subsequent transit-time flowmetric measurement indicating satisfactory blood flow values. We have no possibility to perform an intraoperative coronary angiography and that is why we are not aware of the percentage of the falsely-satisfactory results in our patients.

From January 2012 to December 2015, 189 patients, aged 50.6±6.0 years, 173 males and 16 females, undergo first isolated coronary artery bypass grafting surgery with the *in situ* skeletonized left internal thoracic artery grafting to the left anterior descending coronary artery with a mean length of 18.6±1.2 cm (between 17.0 and 22.0 cm) (Q. Ji *et al*., 2018). Intraoperative graft blood flow of the graft is 42±9 mL/min. (between 18 and 72 mL/min.) is associated with pulsatile index of 0.8-4.3. In-hospital mortality is 0.5%. Postoperative morbidity includes acute myocardial

infarction (0.5%), stroke (0.5%), and deep sternal wound infections (1.1%). The mid-term survival rate is 97.2% and the incidence of repeat revascularization is 0.6%. The patency rate of the graft to the left anterior descending coronary artery is 97.1% by CT angiography examination during the follow-up period of 23.2±9.7 months. Logistic regression analysis shows that intraoperative graft blood flow has an independent influence on the risk of the mid-term graft failure.

The only patients of ours undergoing isolated revascularization of the anterior descendent coronary artery by means of the left internal thoracic artery are those who undergo a minimally invasive myocardial revascularization. Among the patients operated on according to plan, there are no complications such as postoperative myocardial infarction, stroke and deep wound infections. Some 32 out of 33 arterial grafts (97% of the cases) of the left internal thoracic artery are patent during the follow-up examination by using CT-assisted angiography between six and 23 months after surgery. The values of the intraoperative blood flow and pulsatile index in the graft measured by us (of 10 mL/min. and 4.2) are associated with graft failure during the follow-up.

5.3. Clinical application of coronary angiography in conventional CAB and CAB on a 'bearting heart'

In our opinion, CT-assisted coronary angiography is irreplaceable when performing the control examinations to establish graft patency in the patients without any clinical and historical data about myocardial ischemia during the postoperative period.

P. T. Moore *et al*. (2018) analyze the long-term results in 17316 patients undergoing CAB at a mean age of 65.7±9.8 years in British Columbia, Canada, during the period between 2001 and 2009 inclusive and followed-up until the end of 2013. At a median follow-up of 8.5 (range 4.0 to 12.9) years, 3185 patients (18.4%) have died, 3135 (18.1%) undergo repeated coronary angiography with or without PCI or repeated CAB, and the rest 10996 patients (63.50% of the cases survive without additional procedures. Some 1459 patients (46.54% of the cases) who have undergone coronary angiography undergo further revascularization. The results from the multivariate analysis demonstrate that haemodialysis dependency and age over 75 are the strongest predictors of long-term mortality rate, whereas left internal thoracic artery utilization and aspirin therapy play a protective role. The repeated revascularization can predict patients' survival (adjusted hazard ratio 0.76; 95% confidence interval, 0.63-0.92; p=0.004).

Only thirty three out of a total of more than 100 patients of ours asked in a phone call for a control examination of the patency of their grafts respond to this invitation. All of them prefer the accomplishment of CT-assisted coronary angiography to standard invasive coronary angiography.

Preoperative thoraco-abdominal multidetector CT angiography is performed between 2014 and 2016 in 443 out of a total of 456 patients (in 97.15% of the cases) undergoing isolated CAB (K. J. Na *et al*., 2018). In 208 patients (in 46.95% of the

cases), 292 clinically significant incidental pathological findings are established affecting the perioperative management, i. e. 231 atherosclerotic findings in 176 patients and other 61 miscellaneous findings in 61 patients. Twenty-nine patients have both findings simultaneously. According to multivariable analysis, advanced age, chronic renal failure, recent acute myocardial infarction, and left ventricular dysfunction are predisposing factors for the occurrence of significant incidental findings.

The patients with operative heart diseases hidden a risk of occurrence of perioperative complications associated with the presence of paracardiac diseases which not seldom remain without any clinical manifestation. Generalized atherosclerosis in the patients undergoing cardiac surgery can cause ischemic cerebral and peripheral vascular accidents etc. Sometimes during the intraoperative or immediate early postoperative period in these patients, it is necessary to implant a heart supporting system, e.g. intraortic balloon pump. In such cases, preoperative CT-assisted thoraco-abdominal CT angiography could 'see' significant incidental pathological findings such as severe atherosclerotic alterations along the peripheral arteries and, in this way, it could protect the patient from the development of serious postoperative complications. We perform the preoperative CT angiography for peripheral vascular status assessment of the patients with history of peripheral vascular disease and Doppler sonographically proved absence of a peripheral arterial pulse. Seven patients undergoing CAB with CPB necessitate intraoperative implantation of the intraaortic balloon pump. In six of them, this implantatuion is standard one - through the left or right common femoral artery. In one patient, an alternative of the location for implantation is looked for such as the ascendent aorta because of the severe atherosclerotic alterations of both femoral arteries detected during the attempts for this implantation. This example of an atypical implantation of the intraaortic balloon pump demonstrates how the accomplishment of the preoperative thoraco-abdominal CT angiography and the detection of the significant incidental pathological findings in this kind of patients could save up valuable operation time and could avoid the development of of serious postoperative complications.

F. Jungmann *et al.* (2017) analyze 13 reports published between 2007 and 2016 and dealing with assessment of graft patency after CAB surgery using 64-slice CT angiography. Multidetector CT angiography with ECG and conventional invasive coronary angiography are compared in the evaluation of the patency of a total of 2521 grafts in 1002 patients and the identification of the stenoses in them of >50%. The sensitivity of the multidetector CT angiography with ECG is 97.2%; the specificity is 97.5%; the positive predictive value is 99% and the negative predictive value is 93.6%.

Graft patency assessment one year after CAB and CAB on a 'beating heart' is compared by means of ≥64-slice CT coronary angiography within a prospective multicenter randomized pilot study of a total of 512 grafts in 157 patients (CAB is done in 73 patients while CAB on a 'beating heart' is performed in 84 patients (N. Noiseaux *et al*., 2017). Patency index (percentage of nonoccluded grafts) for the CAB

is statistically insignificantly greater for the first method (95% versus 89%; p=0.09). Patency is similar for arterial and vein grafts (both 92%; p=0.88). There is no difference between target territories (89% versus 94%; p=0.53).

Postoperative CT coronary angiography is performed in 33 of our patients, in 16 undergoing conventional CAB and 17 after CAB on a 'beating heart'. A total of 48 grafts in the patients from the first group and 52 grafts in those from the second one are controlled. Our results are comparable with those reported by N. Noiseux *et al.* (2017). Patency index is statistically insignificantly greater in the patients from the first group than in those in the second one (91.7% versus 84.6%). The patency of the arterial and venous grafts is similar in both methods, too (92.1% versus 87.5% for the arterial and 90% versus 75% for the venous grafts; p=0.168).

M. Yamamoto *et al.* (2017) compare the results from the application of the HyperEye Medical System angiography using indocyanine green to visualize blood vessels in CAB with with those of fluoroscopic coronary angiography in 177 grafts of 69 patients. Grafts in the patent and failed groups show significant differences in their increasing rate of indocyanine green intensity and average acceleration value. The average acceleration value of this intensity of internal thoracic artery and saphenous vein grafts are 112.3 and 144.9 intensity/s^2 in the patent grafts and 71.0 and 91.8 intensity/s^2 in the failed ones.

The experience of various authors when performing the coronary angiography during the early postoperative period is of interest.

Urgent postoperative coronary angiography is accomplished between January 2005 and June 2011 in 106 out of a total of 6025 patients (in 1.76% of the cases) undergoing isolated or combined CAB (F. Fleißner *et al*., 2017). The average time between the cardiac operation and the coronary angiogram is 3.41±5.68 days. The examination is performed in 25 patients after total arterial CAB (in 1.3%), in 65 patients - after combined arterial and venous CAB (in 2%) and in 16 patients - after venous CAB only (in 1.8% of the cases). CAB revision is done in 24% while percutaneous transluminal coronary angioplasty, stenting, or both procedures are performed in 32% of the patients.

Within a retrospective observational study of a total of 4446 patients at a mean age of 68±9 years undergoing CAB between 2007 and 2012, K. Hultgren *et al.* (2016) perform urgent coronary angiography in 87 patients (in 1.96% of the cases). There are pathological angiographic findings in 60% of the patients representing electrocardiographic changes (in 92%), echocardiographic changes (in 48%), haemodynamic instability (in 28%), angina pectoris (in 15%) and/or arrhythmia (in 13% of the cases). In the patients assessed by angiography, there is a statistically reliably higher 30-day mortality rate (7% versus 2%; p=0.002) and lower five-year survival rate (77% versus 87%; p=0.043) than in the rest patients.

Between January 2004 and December 2010, P. M. Davierwala *et al.* (2013) perform isolated CAB in 7461 patients. Because of perioperative myocardial ischemia, emergent coronary angiography is performed in 3499 of them (in 5.35% of the cases) of a total of 900 grafts in 255 patients as well as 1061 distal anastomoses are accomplished. Revision of CAB is carried out in 130 of these patients (in 50.98%

of the cases). In-hospital mortality is statistically significantly higher among the patients with perioperative myocardial ischemia than among the rest patients (7.3% versus 2.9%; p<0.001). The in-hospital mortality of the patients with perioperative myocardial ischemia is 9.4% in case of a pathological angiographic finding and 3.5% in normal one as this difference is statistically significant, too (p=0.03). Five-year survival rate of the patients without any perioperative myocardial ischemia is statistically significantly better than that of the patients with perioperative myocardial ischemia and a pathological angiographic finding (85.7±0.5% versus 74.9±2.9%; p<0.001 log-rank).

The therapeutic strategy based on coronary angiography findings reduces the burden of high mortality rate of myocardial ischemia patients after CAB (J. Szavits-Nossan *et al*., 2012).

Between 2003 and 2009, M. Laflamme *et al*. (2012) perform isolated CAB in 5598 patients. Early coronary angiography is accomplished in 39 of them (in 0.70% of the cases) because of suspected perioperative myocardial ischemia. Early graft failure is detected in 32 patients (in 82.05% of the cases).

We do not encounter any signs of perioperative myocardial ischemia requiring the consideration and accomplishment of emergent control postoperative selective coronary angiography. We have elaborated a protocol according to which the patients with suspected postoperative myocardial ischemia are timely discussed by a 'heart team' consisting of cardiac surgeon, intensive care specialist and invasive cardiologist and thus the indications for the execution of the emergent selective coronary angiography are defined as the latter will determine the behaviour - CAB revision or drug therapy.

5.4. Clinical significance of cardiac troponin-I and CK-MB in conventional CAB and CAB on a 'beating heart'

The comparison of the mean values of cardiac troponin-I and CK-MB in our patients by means of independent samples *t*-test reveals a statistically significant difference between on-pump- and off-pump-operaions (*t*=4.191; p=0.0001 and *t*=4.701; p=0.0001, respectively).

At the same time, not only between cardiac troponin-I mean values, on the one hand, and those of blood flow and pulsatile index, on the other hand, but also between mean CK-MB values, on the one hand, and those of blood flow and pulsatile index, on the other hand, there are no statistically significant correlations. This determines the importance of blood flow values during the flowmetric examination of the quality of the anastomosis accomplished. Data about enzyme release play a subordinate role.

Progression of coronary artery disease is assessed in 717 patients who have undergone ≥2 coronary angiographic examinations at least three months before surgery (A. Samman Tahhan *et a*l., 2018). There is a normal finding in 11%, nonobstructive coronary artery disease - in 23%, one- or two-vessel disease - in 20%, and multivessel disease - in 26% of the cases. After adjusting for age, sex, race, body mass index, tobacco smoking, arterial hypertension, diabetes mellitus history, and

renal function, an independent association between high-sensitivity troponin-I concentrations not only with the severity of the coronary artery disease measured by the Gensini score (log 2 ß=0.31; p<0.001) but also with disease progression (log 2 ß=0.36; p<0.001) is established. Besides the high-sensitivity troponin-I is a significant predictor of incident death, cardiovascular death, myocardial infarction, revascularization, and cardiac hospitalizations.

The effect of remote ischemic preconditioning on cardiac troponin I release due to myocyte necrosis is studied in 28 patients undergoing elective CAB six and 24 hours after surgery (F. Javaherforoosh Zadeh *et al.*, 2017). Cardiac troponin I at six hours after preconditioning is statistically significantly lower compared to the control group (p=0.036) and even after 24 hours (p<0.05).

We consider the remote ischemic preconditioning inapplicable in our practice because of the fact that according to the results from numerous investigations of a limited number of patients undergoing cardiosurgical interventions, there are no categorical data about a significant influence of cariac enzyme release when applying the protocol for this examination. In addition, both large randomized clinical trials such as ERICCA (covering 1612 patients in Great Britain) (D. J. Hausenloy *et al*., 2015) and RIPHeart (covering 1403 patients in Germany) (P. Meybohm *et al*., 2015) do not confirm its effect at all.

Between 2004 and 2012, a total of 5318 patients without evidence of preoperative myocardial ischemia undergo a number of cardiac surgical interventions ranging from isolated coronary revascularization to combined valve CAB (A. T. Mokhtar *et al*., 2017). The unadjusted in-hospital mortality rate is 3.3% (175 deaths). Four categories of peak serum cardiac troponin levels are identified: ≤0.6 ng/mL; between 0.7 and 1.9 ng/mL; between 2.0 and 3.1 ng/mL and >3.1 ng/mL. The following unadjusted mortality rates of 1.0%, 3.6%, 10.1%, and 33.1% are established, respectively. The results from the multivariate logistic regression analysis demonstrate that all peak serum cardiac troponin levels greater than 0.6 ng/mL as a manifestation of myocardial ischemia are independent predictors of in-hospital mortality in a dose-dependent manner. Our own results differ from those reported by A. T. Mokhtar *et al*. (2017). It is noteworthy that the number of our examined patients is smaller than that of the other authors. In 55 out of 64 patients of ours (in 85.9%) undergoing CAB and in 72 out of 79 patients of ours (in 91.1% of the cases) undergoing CAB on a 'beating heart', data about preoperative myocardial ischemia are absent. Among these patients, there are no lethal cases during the hospital stay. The mean peak cardiac troponin levels are 11.2 ng/mL in the fist group and 3.06 ng/mL in the second one.

A total 202 multivessel coronary artery disease patients of which 90 (44.55% of the cases) are with diabetes mellitus undergo percutaneous intervention, conventional CAB and CAB on a 'beating heart' (P. C. Rezende и съавт., 2017). Troponin and CK-MB are systematically assessed at baseline and after six, 12, 24, 36, 48 and 72 hours. Peak mean postoperative troponin values in the patients with and in those without diabetes mellitus are 2.18 ng/mL (between 0.47 and 5.14 ng/mL) and 2.24 ng/mL (between 0.69 and 5.42 ng/mL) (p=0.81), respectively, whereas such

CK-MB levels are 14.1 ng/mL (between 6.8 and 31.7 ng/mL) and 14.0 ng/mL (between 4.2 and 29.8 ng/mL) (p=0.43), respectively. Diabetes mellitus is not not associated with a higher risk of myocardial injury after myocardial revascularization.

A total of 46 of our patients (32.2% of the cases) present with coronary artery disease and accompanying diabetes mellitus. Troponin-I and CK-MB are examined prior to operation and six, 12, 24 and 36 hours after it. The maximal mean postoperative troponin values in the patients with and in those without diabetes mellitus are 9.29 ng/mL (between 0.2 and 144 ng/mL) and 13.75 ng/mL (between 0.42 and 106 ng/mL) (p=0.391), respectively, while the maximal mean CK-MB values are 42.43 U/L (between 9 and 131 U/L) and 65.18 U/L (between 18 and 447 U/L), respectively. CK-MB levels are statistically reliably lower in diabetes mellitus patients (p=0.037).

The concentrations of the cardiac troponin I, high-sensitivity cardiac troponin and CK-MB isoenzyme mass are examined just before aortic cross-clamping and after aortic declamping in 37 patients at a mean age of 63.4±8.9 years, 24 males and 13 females, undergoing elective CAB (E. F. Kocak *et al*., 2015). Perioperative myocardial injury and apoptosis is observed in all the patients operated on. The concentrations of these cardiac markers increase statistically significantly after aortic declamping in terms of CK-MB isoenzyme activity and mass ($p<0.001$) cardiac troponin I ($p<0.01$), and high-sensitivity cardiac troponin ($p<0.05$). There is a positive correlation dependence between apoptotic index, on the one hand, and cardiac troponin I ($r=0.611$; $p<0.001$) and high-sensitivity cardiac troponin ($r=0.806$; $p<0.001$), on the other hand; myocardial injury score, on the one hand, and cardiac troponin I ($r=0.544$; $p<0.001$) and high-sensitivity cardiac troponin ($r=0.719$; $p<0.001$), on the other hand, during the period after aortic declamping. One observes positive correlations not only between apoptotic index ($r=0.507$; $p<0.001$) and myocardial injury score ($r=0.416$; $p<0.010$), on the one hand, and high-sensitivity cardiac troponin release, on the other hand, but also between aortic cross-clamping time ($r=0.448$; $p<0.007$) and CPB time ($r=0.342$; $p<0.047$), on the one hand, and high-sensitivity cardiac troponin release, on the other hand.

We consider unduly the additional examination of the cardiac enzyme values prior to aortic cross-clamping and immediately after aortic declamping. The results from the enzymatic examinations in our Clinic just after patient's bringing out from the operation theatre demonstrate the extent of the perioperative myocardial injury which depends on aortic cross-clamping time.

We select at random 26 patients without any preoperative myocardial ischemia and divide them into two groups - with aortic cross-clamping time up to 75 min. and over 75 min. The mean cardiac troponin I value is statistically significantly lower at cross-clamping time up to 75 min. (3.43±2.02 ng/mL) than at cross-clamping time over 75 min. (12.27±11.94 ng/mL; p=0.018).

Within a prospective study, the serum concentrations of two new biomarkers to detect myocardial injury shortly after onset of ischemia, i.e. heart-type fatty acid binding protein and ischemia-modified albumin, are comparatively assessed versus cardiac troponin I in 210 consecutive patients undergoing isolated CAB

preoperatively and during the first 72 hours after surgery (M. Thielmann *et al.*, 2017). Perioperative myocardial infarction is defined in 14 out of a total of 108 patients with an examined heart-type fatty acid binding protein and cardiac troponin I. There are statistically significantly higher values of both parameters in the patients with perioperative myocardial infarction ($p<0.001$). The values of the heart-type fatty acid binding protein differ already at the first hour after surgery ($p<0.001$). There is a perioperative myocardial infarction in 18 out of a total of 102 patients with examined ischemia-modified albumin and cardiac troponin I, however, there are no significant differences.

Z. Wang и съавт. (2018) examine the circulating microRNAs (1, 133a, 208a и 499) and several cardiac and inflammatory factors such as CK-MB, brain natriuretic peptide, cardiac troponin T, interleukin-6, interleukin-8, interleukin-10, high-sensitivity C-reactive protein, and tumour necrosis factor-α in 27 acute coronary syndrome patients prior to and after CAB accomplishment. Following the intervention, there is a statistically reliable increase of the concentrations of microRNA-1 ($p=0.0011$), microRNA-133a ($p=0.0057$) and microRNA-208a ($p=0.01970$) as well as of CK-MB, cardiac troponin T, brain natriuretic peptide and interleukin-6. The microRNA-133a, microRNA-208a and microRNA-499 positively correlate with cardiac troponin T ($r=0.302$; $p=0,027$; $r=0.326$; $p=0.016$ and $r=0.298$; $p=0.029$), respectively, while only the microRNA-208a correlates statistically significantly with CK-MB ($r=0.278$; $p=0.041$). There is also a correlation between the microRNA-133a and the microRNA-208a, on the one hand, and interleukin-6, on the other hand ($r=0.287$; $p=0.036$ and $r=0.292$; $p=0.032$), respectively.

6. CONCLUDING REMARKS

Our study demonstrates for the first time in Bulgaria the need for a wider application of intraoperative transit-time flowmetry for the precise and objective timely diagnosis of the dysfunction of arterial and venous grafts in both conventional CAB and in CAB on a ‘beating heart’ in patients with advanced IHD.

When performing strictly individualized operative interventions taking into consideration a set of specific characteristics such as the presence of a mono-, two- and multivessel coronary heart disease, the choice of an adequate number of grafts from different proper arteries and veins, the assessment of patients’ main haemodynamic patterns and severe accompanying diseases we could warrant a sufficient clinical effectiveness of our complex behaviour. The comparative analysis of the mean values of routine operative indicators such as duration of operation, pre- and post-operative left ventricular EF, number of anastomoses etc., of two conventional laboratory parameters such as cardiac troponin-I and CK-MB as well as of the modern haemodynamic parameters such as coronary blood flow, pulsatile index and wave morphology originally introduced in Bulgaria in combination with coronary angiography convincingly proves that the CAB on a ‘beating heart’ is not inferior to the conventional CAB.

Our personal clinical case reports convincingly demonstrate the considerable diagnostic and prognostic value of the intraoperative transit-time flowmetry when making the proper decision about the true necessity of timely revision of the obstructed coronary graft in accordance with the foreign experience recently gained worldwide. In this way, the behaviour towards to the patients with advanced IHD could be optimized.

7. CONCLUSIONS

Based on the comprehensive results obtained by us and data from the foreign literature available we could draw the following main **conclusions**:

1. The dynamic follow-up of the values of the coronary blood flow and pulsatile index as well as of wave morphology registered by means of intraoperative transit-time flowmetry enables the timely prognostication of the postoperative outcomes in CAB on a ‘beating heart’ and conventional CAB.

2. We establish statistically significant correlation dependences between the coronary blood flow values and the pulsatile index ones in the arterial grafts as well as between the number of corrupted coronary arteries and the blood flow in the venous grafts in all the patients with CAB on a ‘beating heart’.

3. We establish statistically significant correlation dependences between the CAB on a ‘beating heart’ and conventional CAB in terms of the mean values of the cardiac troponin-I and CK-MB.

4. We establish a statistically significantly shorter operation time in the patients undergoing CAB on a ‘beating heart’ than those undergoing conventional CAB usage.

5. Thanks to the modern method of intraoperative transit-time flowmetry introduced in our cardiosurgical practice it becomes possible to timely recognize the functional deficit of the coronary blood flow in the arterial grafts and this to accomplish their revision within acceptably short terms.

6. The several-years long results from the application of the methods of CAB on a ‘beating heart’ and conventional CAB in a large number of patients of ours with advanced IHD and a series of accompanying diseases achieved by us are proved very good.

8. LIST OF PUBLICATIONS RELATED TO THE DISSERTATION

1. **Kornovski V**. A scientometric study on the topic of the coronary arterialbypass grafting. *Medical Magazine*. 2017, No 10, 18-22 (in Bulgarian).
2. **Kornovski V**, Panayotov P. Intraoperative flowmetry for graft assessment in coronary artery bypass grafting. Our experience. *Scripta Scientifica Medica*. **49**, 2017, No 4, 73-78.
3. **Kornovski V**, Panayotov P, Angelov A, Gradinarov C, Slavov M, Peychev Y, Bachvarov G. Benefits of off-pump coronary artery bypass grafting in patients older than 75 years of age. *Euro-Asian Journal of Surgery and Medicine*. **2**, 2018, No 1, 1-6.
4. **Kornovski V**, Panayotov P, Angelov A, Gradinarov Ts. Transit-time flowmetric evaluation of coronary artery bypass graft flow after off- and on-pump myocardfial revascularization. *Scripta Scientifica Medica*. **50**, 2018, No 3, 30-36.

9. CONTIBUTIONS OF THE DISSERTATION

Original scientific and applicable contributions

1. Introduction and substantiation of the application of the contemporary method of intraoperative transit-time flowmetry for precise, objective and timely evaluation of the usage of CAB on a ‘beating heart’ and conventional CAB in advanced IHD patients.

2. An algorithm for performance of the transit-time flowmetry and definition of the indications for graft revision according to the flowmetric results is approved.

3. Some statistically significant correlation dependences between the coronary blood flow values and the pulsatile index ones in the arterial grafts as well as between the number of damaged arteries and the blood flow in the venous grafts in the patients with CAB on a ‘beating heart’ are approved.

4. Some statistically significant correlation dependences between the CAB on a ‘beating heart’ and conventional CAB in terms of the mean values of both cardiac troponin-I and CK-MB are established.

Contributions of confirmatory nature

1. Our hypothesis that the method of CAB on a ‘beating heart’ is not inferior to the conventional CAB in advanced IHD patients is confirmed.

2. The role of transit-time flowmetry for optimization of the cardiosurgical behaviour in IHD patients and accompanying diseases is confirmed.

3. The considerable diagnostic and prognostic value of transit-time flowmetry when determining the necessity of timely revision of the impenetrable coronary artery bypass graft is confirmed.

4. The necessity of monitoring of the flowmetric parameters with the purpose of prognostication of the postoperative outcomes in CAB on a ‘beating heart’ and conventional CAB is confirmed.

5. The CT coronary angiography is approved as a method for non-invasive diagnosis of delayed and long-term passability of the coronary artery bypass grafts in IHD after CAB is approved.