Hypothermic Intermittent Cross Clamp Technique; A Retrospective Cohort Analysis of 3729 Isolated Coronary Artery Bypass Grafting

Hipotermik Aralıklı Kros Klemp Tekniği; 3729 İzole Koroner Arter Bypass Greftlemenin Retrospektif Kohort Analizi

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ABSTRACT Objective: Over the years, various techniques have been used in an attempt to preserve the myocardium. Intermittent cross clamp technique is being used since the early years of cardiac surgery. In this study, mortality, morbidity (mainly due to cardiac and neurological complications) and factors contributing to them were evaluated in patients who had coronary arterial bypass graft using hypothermic intermittent cross clamp technique. **Material and Methods:** Between January 2002 and December 2007, 3729 isolated coronary bypass operations were performed using hypothermic intermittent cross clamp technique by the same team. Mean age of the cases was 64.97±9.38 years, and the ratio of female patients was 23,4% (872). The patients had the following pre-existing conditions; diabetes mellitus 19.8% (738), hypertension 55.8% (2081), chronic obstructive pulmonary disease 3.2% (121), pre-operative neurological disorder 3.5% (131), advanced left ventricular failure 6.7% (248), and the ratio of patients who had emergency operation was 1.7% (63) while the ratio of those who had high risk (Euroscore ≥ 6) was 4.7% (176). **Results:** Hospital mortality rate was 95 patients (2.5%). Fifty-two (1,4%) patients were lost due to cardiac causes, 22 (0.6%) due to neurological causes and 21 (0.5%) due to other reasons. Multivariate logistic regression analysis revealed the following variables to be independent risk factors: age, left ventricular dysfunction, bypass time, emergency operation and duration of stay in intensive care unit. **Conclusion:** Considering its ease of application, type of target vessel and its contributions to the operational comfort of the surgeon, this technique can be recommended for coronary artery bypass surgery.

Key Words: Coronary artery bypass; constriction

ÖZET Amaç: Yıllar boyunca, miyokard korumasında çeşitli teknikler kullanılmıştır. Aralıklı kros klemp tekniği, kardiyak cerrahinin erken dönemlerinden beri kullanılmaktadır. Bu çalışmada, hipotermik aralıklı kross klemp tekniği kullanılarak, koroner arteriyel bypass greft yapılan hastalarda mortalite ve morbidite (ağırlıklı olarak kardiyak ve nörolojik komplikasyonlara bağlı olan) ve bunlara etki eden faktörler açısından değerlendirildi. **Gereç ve Yöntemler:** Ocak 2002-Aralık 2007 tarihleri arasında 3729 izole koroner bypass operasyonu, aynı ekip tarafından hipotermik aralıklı kross klemp tekniği ile gerçekleştirildi. Ortalama yaş 64,97 ± 9,38 yıl olup, hastaların %23,4 (872)'ü kadındı. Diabetes mellitus %19,8 (738), hipertansiyon %55,8 (2081), kronik obstrüktif akciğer hastalığı %3,2 (121), preoperatif nörolojik bozukluk %3,5 (131), ileri derece sol ventrikül yetmezliği %6,7 (248), acil operasyon gereksinimi %1,7 (63) ve yüksek riskli (Euroscore ≥ 6) hasta oranı %4,7 (176) idi. **Bulgular:** Hastanede ölüm oranı 95 (%2,5) hastadır. Kardiyak sebeplerden 52 (%1,4), nörolojik sebeplerden 22 (%0,6) ve diğer nedenlerden 21 (%0,5) hasta kaybedilmiştir. Multivaryat logistik regresyon analizi ile bağımsız risk faktörleri olarak yaş, sol ventrikül disfonksiyonu, baypas süresi, acil operasyon, yoğun bakım süresi saptanmıştır. **Sonuç:** Bu teknik; uygulama kolaylığı, hedef damarın yapısı ve cerrahın çalışma konforuna katkıları göz önüne alındığında, koroner arter bypass olgularında güvenli bir şekilde kullanılabilir.

Anahtar Kelimeler: Koroner arter baypas; daralma

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Over the years, various techniques have been used in an attempt to preserve the myocardium. Cold blood cardioplegia is probably the worldwide standard used by the majority of surgeons. It was implemented for the first time by Melrose et al. in 1955.[1] For cardioplegia, it is not possible to argue that it is always the perfect/optimal method on its own because of variability of content (crystalloid, blood, hyperkalemic, nornokalemic) and practices (antregrade, retrograde, intermittent, continuous).

For myocardial protection, intermittent cross clamp technique and on-pump/beating heart bypass technique are known as alternative approaches. Intermittent cross clamp technique is being used since the early years of cardiac surgery. A respectable minority of surgeons is still using intermittent aortic cross clamping for myocardial protection, The method of intermittent aortic cross-clamping is based on moderate hypothermia (27-30 °C). This allows the effects of a short period of ischemia (less than 20 minutes) to be rapidly reversed by reperfusion with normal blood. Despite uncertain results in human myocardium[2] it was indicated that ischemic preconditioning provided by intermittent cross clamp technique is effective in myocardial protection.[3]

In this study, mortality, morbidity (mainly due to cardiac and neurological complications) and factors contributing to mortality and morbidity were evaluated in the patients that had coronary bypass with the hypothermic intermittent cross clamp technique.

MATERIAL AND METHODS

Between January 2002 and December 2007, 3729 isolated coronary bypass operations were executed by using hypothermic intermittent cross clamp technique. All descriptive information about the patients was collected retrospectively from hospital database.

Mean age of the cases was 64.97 ± 9.38 years, and the ratio of female patients was 23.4% (872). The patients had the following pre-existing conditions; diabetes mellitus (DM) 19.8% (738), hypertension (HT) 55.8% (2081), chronic obstructive pulmonary disease (COPD) 3.2% (121), pre-operative neurological disorder 3.5% (131), advanced left ventricular failure (LVF) 6.7% (248), and the ratio of patients who had emergency operation was 1.7% (63) while the ratio of those who had high risk (EuroSCORE ≥ 6) was 4.7% (176).

Average cross clamp (CC) duration was 33.89 ± 14.62/minutes, average bypass (BP) duration was 81.57 ± 36.78/minutes and average number of distal anastomosis was 2.31 ± 0.89. Mean duration of intensive care unit (ICU) stay was found as 1.74 ± 3.51/day. Demographical properties and operational findings of the patients were given in Table 1.

Carotid Doppler scanning was performed all of the patients. If there are obstruction 75% in carotid arteries, corotid endarterectomy was committed. All patients underwent preoperative transthoracic echocardiography and intraoperative transesophagial echocardiography. Preoperative heparin therapy was initiated to surgery patients who are diagnosed intracardiac thrombus. All these patients who have intracardiac thrombus, atrial fibrillation, carotid obstruction or atherosclerosis were found in the ascending aorta by

TABLE 1: Demographic and operation characteristics of the patients.

Demographic characteristics		
Mean age (mean±SD) (year)	64.97 ± 9.38	
Female/male (n; %)	872/2857	76.6/23.4%
Diabetes mellitus (n; %)	738	19.8%
Hypertension (n; %)	2081	55.8%
Chronic obstructive lung disease (n; %)	121	3.2%
Preoperative neurological dysfunction (n; %)	131	3.5%
Left ventricular dysfunction (EF < 30) (n; %)	248	6.7%
Emergency operation (n; %)	63	1.7%
Euroscore value ≥ 6 (n; %)	176	4.7%
Operation characteristics		
Mean cross clamp time	33.89 ± 14.62/minute	
Mean bypass time	81.57 ± 36.78/minute	
Mean number of distal anastomosis	2.31 ± 0.89	
Mean duration of stay in intensive care unit	1.74 ± 3.51/day	

transesophageal echocardiography in operation omitted from our study.

EuroSCORE (European System for Cardiac Operative Risk Evaluation): It is a risk model which allows the calculation of the risk of death after a heart operation. Additive version of the score was originally published. This score could be easily calculated at the bedside. The additive EuroSCORE is simple, well validated, user-friendly and works at the bedside without specialised equipment.

SURGICAL TECHNIQUE

All of the patients were operated under cardiopulmonary bypass. Membran oxygenator and roller pump were used. Aorta-two stage venous cannulation was performed. Activated clotting time (ACT) was kept between 480-600 seconds after systemic heparinization. Systemic heat was lowered to 30-32°C. Vent was placed to main pulmonary artery for decompression of heart. Heart was fibrillated electrically. Aortic cross-clamp was taken after each distal anastomosis. Proximal anastomosis was performed under lateral clamp. Afterwards, cross was put again and other distal anastomoses were completed. Distal anastomoses were performed with 7-0 polypropylene firstly to right coronary artery (RCA) or posterior descending (PD) bundle branch, secondly to circumflex (Cx) coronary artery system and lastly to left coronary artery (LAD) and diagonal artery (D1). Left anterior mammarial artery (LIMA) was chosen for LAD. [91.2% LİMA, 0. 013% right anterior mammarial artery (RİMA), 0. 002% bilateral mammarian artery (BİMA) were used in patients.] Patients were weaned from cardiopulmonary bypass when the rectal temperature reached 37°C.

POSTOPERATIVE NEUROLOGICAL DYSFUNCTION DIAGNOSIS

In patients with a previous neurological illness, new cerebrovascular event is evaluated on the basis of neurological findings or worsening of the current findings. Diagnosis was made after the evaluation of the radiological findings by a neurologist following the doubts raised by the surgery team. Neurological events or the preoperative dysfunctions were confirmed by a neurologist.

STATISTICAL ANALYSIS

For statistical analysis, SPSS (Statistical Package for Social Sciences) for Windows 15.0 was used. For analysis of study data, in addition to complementary statistical methods (average, standard deviation), Student t test was used for analysis of data with normal distribution in two groups during comparison of quantitative data; Oneway Anova test was used for comparison of three and more groups and Tukey HDS test was used for determination of the group causing significance. For the inter-group comparison of parameters that do not show normal distribution Kruskal Wallis test was used and for determination of the group causing significance Mann Whitney U test was used. And for determining the cut off points of age and cross clamp time variables which had effect on mortality, ROC analysis was used. And for the multivariate analysis of risk factors contributing to mortality, logistical regression method was used. For the comparison of qualitative data, Chi-square test was used. Results were within 95% confidence interval and had a significance level of $p<0.05$.

RESULTS

MORBIDITY

Neurological complications (Stroke-TIA) 88 (2.4%), cardiac complications (myocardial infarct, rhytm disorders, inotrop/intra-aortic balloon pump) 254 (6.8%), other complications (bleeding-hemorrhage, acute renal insufficiency / multi-organ failure, respiratory failure, return to intensive care unit) were seen in 251 (6.7%) cases (Table 2).

TABLE 2: Postoperative complications.

Neurological event	88	2.4
Cardiac event	254	6.8
Per/postoperative MI	59	1.6
Rhytm disturbances	102	2.73
Inotrop usage/IABP	208	5.6
Other	251	6.7
Bleeding/Revision	63	1.69
ARF/MOF	44	1.17
Respiratory failure	89	2.3
Return ICU	145	3.9

MI; Myocardial Infarction, IABP; Intraaortic Balloon Pump, MOF; Multi-organ failure, ICU; İntensive care unit

TABLE 3: Univariate and multivariate ODDS levels of the risk factors having an effect on mortality

	Univariate ODDS (95% CI)	Multivariate ODDS (95% CI)
Age (years) ≥70	3.63 (2.16-6.10)	2.62 (1.47-4.68)
Bypass time	-	1.00 (1.00-1.01)
Cross clamp time ≥ 38	1.86 (1.24-2.81)	-
Left ventricular failure (severe)	7.23 (4.59-11.58)	0.360 (0.19-0.66)
Emergency operation	5.98 (2.76-12.94)	0.264 (0.11-0.63)
Neurological dysfunction before surgery	3.01 (1.48-6.12)	-
Euroscore value (medium risk)	2.80 (1.83- 4.29)	-
Euroscore value (high risk)	2.56 (1.09- 6.03)	-
Intensive care unit duration of hospitalization	-	1.19 (1.14-1.24)
Return to intensive care unit	17.69 (11.16-27.02)	-

MORTALITY

Hospital mortality rate was 95 patients (2.5%). Fifty two (1.4%) patients were dead by cardiac causes, 22 (0.6%) for neurological causes and 21 (0.5%) patients lost their lives by other reasons. In this study, as the mortality-related risk factors, average age (64.97), moderate (19.0%) and severe (6.7%) left ventricular insufficiency, emergency operation (1.7%), pre-operative neurological disorder (3.5%), euroSCORE value in high (4.7%) and moderate (26.4%) risk groups, average cross-clamp time (33.89), average bypass time (81.57), return to intensive care (3.9%), development of cardiac and neurological complications and development of mortality were determined to be significantly high ($p<0.001$). There was no statistically significant variation between COPD, DM, gender, average number of distal anastomosis and mortality (Table 3) ($p> 0.05$).

Also, the logistic regression analysis revealed that having an age over 70 increased mortality risk by 2.62 times (95% CI 1.47-4.68) ,while bypass time increased it by 1.007 (95% CI 1.00-1.11) times and, severe left ventricular dysfunction by 0.360 (95% CI; 0.19-0.66) times; emergency operation by 0.264 (95% CI; 0.11-0.63) times; and time spent in intensive care by 1.192 (95% CI; 1.14-1.24) times (Table 3).

DETERMINATION OF THE CUT OFF VALUE OF AGE OVER MORTALITY

There was significant variation in terms of age measurements between cases with and without mortality. With the ROC analysis carried out to determine the cut off point for age, sensitivity in cases aged 70 and above was found to be 81.05%; while specificity was 45.95%; positive predictive value was 3.7% and negative predictive value was 98.93%. Area under the curve was 0.680 (Figure 1).

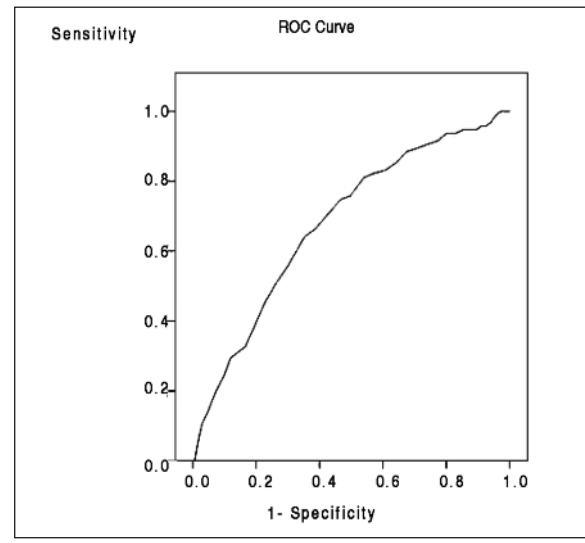

FIGURE 1: ROC curve for the age.
(Area Under the Curve: 0.680; 95% CI: 0.63-0.73)

DETERMINATION OF THE CUT OFF VALUE OF CROSS CLAMP OVER MORTALITY

In cases with and without mortality, there was significant variation between cross clamp measurements. With the ROC analysis carried out to determine the cut off point of the measurement of cross clamp time, sensitivity for cases with cross clamp time of 38 and above was 52.63%;

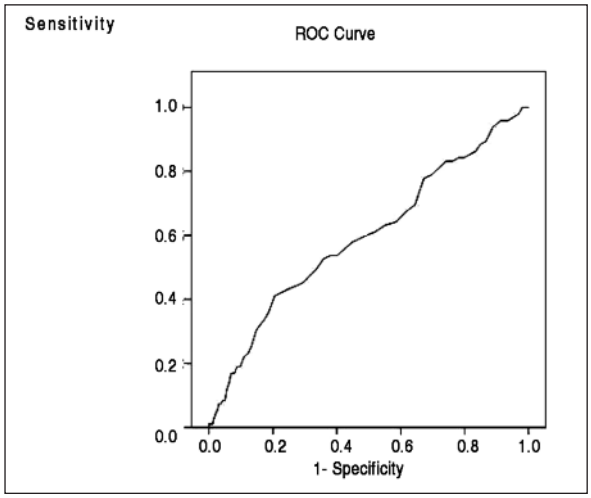

FIGURE 2: ROC curve for the cross clamp time.
(Area Under the Curve: 0.593; 95% CI: 0.53-0.65)

and specificity was 64.23%; while positive predictive value was 3.70% and negative predictive value was 98. 11%. The area under the curve was 0.595 (Figure 2).

EVALUATIONS BASED ON BYPASS NUMBERS

It was determined that the bypass numbers of those patients with cardiac complications were significantly higher than those with no such complication ($p< 0.01$). Based on euroSCORE status, there was a statistically significant difference between bypass numbers ($p< 0.01$). Bypass numbers in the high risk cases were found to be significantly higher than those in the moderate and low risk groups. There was no significant difference between the bypass numbers of those with and without pre-operative neurological dysfunction ($p> 0.05$) (Table 4). Also, there was no statistically significant difference between bypass numbers based on ex causes ($p> 0.05$) (Table 5).

MORTALITY RATES BASED ON EUROSCORE

We used the additive EuroSCORE. The true relationship between risk factors is not additive and the combined impact of two or more risk factors on

TABLE 4: Relation between morbidity and bypass numbers.

		Vein count		
		Av®SD	Median	•p
Preoperative neurological disorder	None	2.30 ± 0.89	2.0	0.087
	Exists	2.44 ± 0.89	2.0	
Cardiac complication	None	2.29 ± 0.89	2.0	0.002**
	Exists	2.47 ± 0.89	2.0	
Neurologic complication	None	2.29 ± 0.89	2.0	0.133
	Exists	2.44 ± 0.86	2.0	
Euroscore value	Low Risk	2.33 ± 0.88	2.0	••0.001**
	Moderate Risk	2.43 ± 0.88	2.0	
	High Risk	2.76 ± 0.87	3.0	

•: Mann Whitney U test ••: Kruskal Wallis test
**p< 0.01.

TABLE 5: Evaluation of bypass numbers based on ex causes.

	Bypass numbers		
Ex Cause	Av ± SD	Median	•p
None	2.30 ± 0.89	2.00	0.218
Cardiac Complication	2.38 ± 0.86	3.00	
Neurological complication	2.50 ± 1.05	2.50	
Other complication	2.61 ± 0.80	3.00	

•: Kruskal Wallis test.

operative risk may be more than the simple sum of their parts, especially when each factor has an important impact on outcome. For most cardiac surgical populations, this discrepancy has little impact on risk prediction as the numbers of such patients are very small (only 176 patients (4.7%) were in high risk group in our study) and the differences seen are not of a magnitude that is sufficient to justify the complex calculations needed to work out the logistic EuroSCORE. Mortality in low risk patients was 1%, but high-risk patients was 17.0% (p= 0.001) (Table 6).

RELATION BETWEEN LEFT VENTRICULAR FUNCTION AND MORTALITY

We determined the mortality rate to be 12.5% in patients with severe left ventricular dysfunction and this was significantly higher than that observed in other group of patients (p= 0.001) (Table 6).

EMERGENCENY CASES RELATED BETWEEN THE MORTALITY

Our emergency mortality rate was 12.7% and this was higher than elective cases (p= 0.001) (Table 6).

DISCUSSION

Cardioplegia is the more commonly used method for myocardial protection during on-pump cardiac surgery. The protective mechanism is based on immediate electromechanical interruption and reduction of cellular metabolism, which preserves cellular energy stores. Blood cardioplegia aims to increase oxygen intake by myocardium, to refill the depleted energy storages and to prolong survival particularly in high risk patients by improving the functioning of myocardium.

The method of intermittent aortic cross-clamping is based on moderate hypothermia (32°C) with a decrease of oxygen demand. With the short ischemic duration (of less than 20 min.), the necessary materials for cells are provided again blood circulation. It is indicated in the studies by Akins,[4] Bonchek et al.,[5] Antunes et al.[6] and Anderson et al.[7] that it is a simple and safe method.

There are only a few prospective randomized trials in the literature dealing with the comparison of both different methods. Pepper et al., revealed no significant differences in myocardial preservation between these methods in patients with at least a good left ventricular function.[8] These results were confirmed by Boncheck et al.[5] Taggart et al.[9] and Cohen et al.[10] could not find any difference between the two methods in terms of myocardial protection when they measured troponin T release and oxygen radical activity. Alex et al. 1454 cases, antegrade and retrograde cold St. Thomas blood cardioplegia studies comparing the technique of intermittent cross clamp fibrillation, have had good results in both groups. In elective and low risk groups, they found the fibrillation technique to be significantly good in terms of cost/efficiency and they proposed it.[11]

TABLE 6: Relation between mortality and euroscore value, left ventricular function, emergency cases.

		Mortality		
		None (n=3634)	Exists (n=95)	p
Euroscore value	Low Risk (≤ 2)	2545 (99.0%)	25 (1.0%)	0.001
	Moderate Risk (2-5)	943 (95.9%)	40 (4.1%)	
	High Risk (≥ 6)	146 (83.0%)	30 (17.0%)	
Left ventricular function	High EF > 50%	2737 (98.8%)	34 (1.2%)	0.001
	Moderate EF= 30-50%	679 (95.6%)	31 (4.4%)	
	Low EF < 30%	218 (87.9%)	30 (12.1%)	
Relation between emergency	Elective	3579 (97.5%)	87 (2.4%)	0.001
	Emergency	55 (87.3%)	8 (12.7%)	

As a result of literature reviews, previous studies reported a low mortality of 1-3%.[6,12,13] Alhan et al.[12] conducted a retrospective analysis of 399 consecutive low-risk patients undergoing first-time CABG using either fibrillation or cold crystalloid cardioplegia for myocardial protection. In their study a prospective randomised trial in 40 consecutive low risk patients were conducted, measuring haemodynamics, enzyme release and ultrastructural changes in left ventricle biopsies. There were no differences in mortality or morbidity between these groups. While their operative mortality was 0.25%, in our study mortality in low risk patients was 1% (Table 6).

In our study, we found that significant risk factors for mortality are: age above 70 years, bypass time, severe left ventricular dysfunction, emergency operation and return to ICU care. With the ROC curve analysis, we determined age over 70 (sensitivity 81.05%, specificity 45.95%) and cross clamp time of 38 minutes and more (sensitivity 52.63%, specificity 64.23%) to be cut-off values.

In elderly patients CABG procedure is becoming increasingly widespread. With increased age, comorbid factors accompany coronary artery disease. In this age group, CABG improves the quality of life and ameliorates the main symptoms. Long-life expectancy is limited.[14] It is known that CABG is a high risk factor for preoperative mortality in advanced ages.[15,16] In the literature, it was determined that there is an independent risk factor in terms of mortality and morbidity.[17] In our study, hypothermic bypass with intermittent cross-clamp, age of 70 is the cut-off value analysis of ROC and 2.62-fold increase in mortality was found after this age.

In their study, Ottino et al.[18] determined age and cross clamp time as independent risk factors for operative mortality. Long perfusion time is known to be related to increased mortality. In a study conducted in relation to this fact, it was demonstrated that perfusion time of over 3 hours is related to mortality.[19] In our study, we determined that bypass time increased mortality by 1.007.

Patients with coronary disease and advanced LVF have a poor prognosis when treated only medically. In various studies have shown that they respond better to coronary surgery.[20-22] The perioperative mortality after CABG in patients with advanced left ventricular insufficiency varies between 2.5-8%.[23-27] In these patients, another alternative treatment is cardiac transplant. However due to lack of sufficient amount of donor organs, it is not used that widespread in such patients. In our study, we determined the mortality rate to be 12.5% in patients with severe left ventricular dysfunction and this was significantly higher than that observed in other group of patients (p= 0.001) (Table 6).

Raco et al. examined 800 patients conducted by a single surgeon who underwent first-time CABG using intermittent cross-clamp fibrillation in a prospective cohort study. Patients were subsequently divided into elective (520), urgent (226) and emergency (54).The mortality rates of 0.57%, 3.09% and 5.55% respectively. Their global mortality was 1. 62%. Subgroup analysis indicated that intermittent aortic cross clamping was a safe and effective technique that allows complete revascularization during both elective and nonelective CABG procedures.[28] In our study, those patients that were operated within 24 hours after presenting at the clinic were considered to be emergency. Our emergency mortality rate was 12.7%. Emergency operation was found to be an independent risk factor that increased mortality by 0.264 folds (Table 6).

Aortic clamping, and, particularly, repeated aortic clamping, is considered one of the major risks for perioperative stroke in patients with atherosclerotic disease of the ascending aorta. However, Musumeci showed that, in patients with no preoperative evidence of aortic or cerebro-vascular disease, the repetitive clamping of the aorta in intermittent ischemic arrest is not associated with a higher rate of cerebro-vascular events compared with the single clamp technique.[27] And in our study, no significant relation was determined between distal anastomosis count which was correlated with cross clamp count and mortality. Rate of neurological complications was 2.4%. Raco et al.,[28] used the technique of intermittent aortic cross-clamping in both elective and nonelective proce-

dures, neurologic disorders were seen mainly in the nonelective patients with a total incidence of stroke of 1.1% and transient ischemic attacks of 0.4% for all comers.

Cold cardioplegia is the common method, used by the majority of surgeons. There are various advantages and disadvantages of cardioplegia. Periods in excess of 20 min were a constant practice which, in the light of more recent knowledge, caused irreversible damage to a significant number of myocardial fibres.[29] These remain some concern about the incapacity of cardioplegic solutions to reach myocardial territories beyond critical coronary artery obstructions.[30] The presence of the cardioplegia and decreases its capacity to protect the myocardium.[31] Another important point to consider is that contact between hypercalemic solutions, sanguineous or assanguineous, and the endothelium of both the native coronary arteries and of the grafts.[32]

Intermittent aortic cross clamping is an easy method to use in coronary artery surgery. It avoids the haemodilution, which results from multidose crystalloid cardioplegia and, to some extent, from blood cardioplegia. As a result of this coagulation factor dilution does not occur and perioperative blood loss is reduced. Easy to apply and operative field more manageable.[6]

As a result, in cases of age over 70, euroSCORE high-risk group, emergency operation, severe left ventricular dysfunction and preoperative neurological dysfunction, hypothermic intermittent cross clamp technique might pose risks in terms of mortality and morbidity. Also in such cases, especially when there is multi-vessel diseases (cross clamp time > 38 min.), mortality risk can be higher. Considering its ease of application, type of target vessel and its contributions to the operational comfort of the surgeon, this technique can be recommended for coronary artery bypass surgery.

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