

Comparison of Perioperative Perfusion - Pressures in terms of Postoperative Morbidity in Coronary Surgery

Saqib Anwar

Cardiac Surgery Section, Tahir Heart Institute, Pakistan

ABSTRACT

Continuum of Perfusion Pressures were compared in terms of Renal Dysfunction, Neurological injury / Stroke, ICU stay, and Mortality in elective coronary surgery cases. It was a prospectively conducted study from March 2014-Feb2017. Total Patients (N=467) underwent on-pump coronary artery bypass grafting (CABG) for 3Vessel Coronary Artery Disease (VCAD =55%), Left Main Stem (LMS=18%), Left Main Equivalent / Proximal Left Anterior Descending Artery (LAD) lesions (17%), N STEMI with ongoing ischemia (2.5%), 1-2 VCAD with inducible ischemia/ large myocardium at jeopardy (5%) and 2-3VCAD with low Ejection Fraction (EF=2.5%) during this period with either Higher perfusion pressures (>75mmHG)=($n_1=260$) or Lower perfusion pressures (<70mmHG)=($n_2=207$). Statistical analysis was conducted with SPSS 16.0. ICU (Intensive Care Unit) prolonged stay (>7 days) was significantly higher in (n_2) -group as compared to (n_1) group ($p<0.05$). Mortality was 3% in Lower Perfusion (n_2) group and 1.5% in Higher Perfusion (n_1) group. Statistically significant Renal Dysfunction (Stage 2-3 RIFLE criteria) and perioperative neurological injury were noted in Lower perfusion- group. But no significant difference was found amongst two in terms of occurrence of Stroke ($p<0.09$). Ambivalent data was collected as regards the Perioperative MI, Low cardiac output (CO) and Mechanical inotropic support-requirements for two groups. However Ventilatory dependence (>5 days) was slightly higher in Lower perfusion group (n_2), though it never reached significant levels ($p>0.05$). Overall study was indicative of favouring Higher perfusion pressures on-pump for better outcomes related to CABG surgery.

Keywords

Coronary Artery Bypass Grafting, Perfusion Pressures, Renal Dysfunction, Neurological injury, ICU stay, Intra-Aortic Balloon Pump (IABP) - requirement, Mortality, Stroke, Low CO, Prolonged -Ventilation, Post - Operative Cognitive Dysfunction (POCD).

1. INTRODUCCION

Coronary Surgery no doubt has evolved to the umpteen standards of unbelievable miraculous developments over the second half of the last century, but conventional on-pump CABG (Fig1.1) still remains the most widely disseminated choice of surgeons round the world today. The perfusion pressures on- bypass perioperatively have had been the point of debate for the past four decades with slightly ambivalent picture glooming around the precise perfusion pressures, though strong evidence and weight of statistics hangs in favour of higher Periop - perfusion pressures for better outcomes in coronary cases in terms of overall morbidity, neurological outcomes and post- bypass renal recovery¹.

The associated neurological injury including (Type I & II neurological deficits) although mostly have had been attributed to micro-embolization on cardiopulmonary bypass (CPB), lower perfusion pressures which off-coursre have also been under constant kaleidoscopic panorama, have had been extensively studied and recently alluded to as possible determinant of myriad of neurological injuries including cerebral gross infarcts as well as water shed infarcts proven on imaging modalities by few studies^{2,3}.

These neurological deficits (including Type 1 & 2 deficits) have been reported as 1-5% incident as per world over contemporary data regarding on-CPB coronary cases. The prevalent data is indicative of far greater prevalence of Type II neurological deficits & cognitive decline in relation to on-pump cerebral hypo perfusion / ischemia than the Type I deficits & Cerebro-Vascular Accidents (CVA)⁸. Whereas Type I neurological deficits are mostly attributed to embolic phenomenon on CPB.

Although cerebral ischemia has not been advocated for mean arterial pressures (MAP) as low as 45-50 mmHg until brain autoregulatory mechanisms are normally functional, yet the accepted guidelines and recommendations world wide are incumbent upon perfusing MAP pressures be ideally 70mmHg and even higher for patients with co-morbidities like Hypertension, Renal Dysfunction or significant neurological history.^{4,5,6,7}

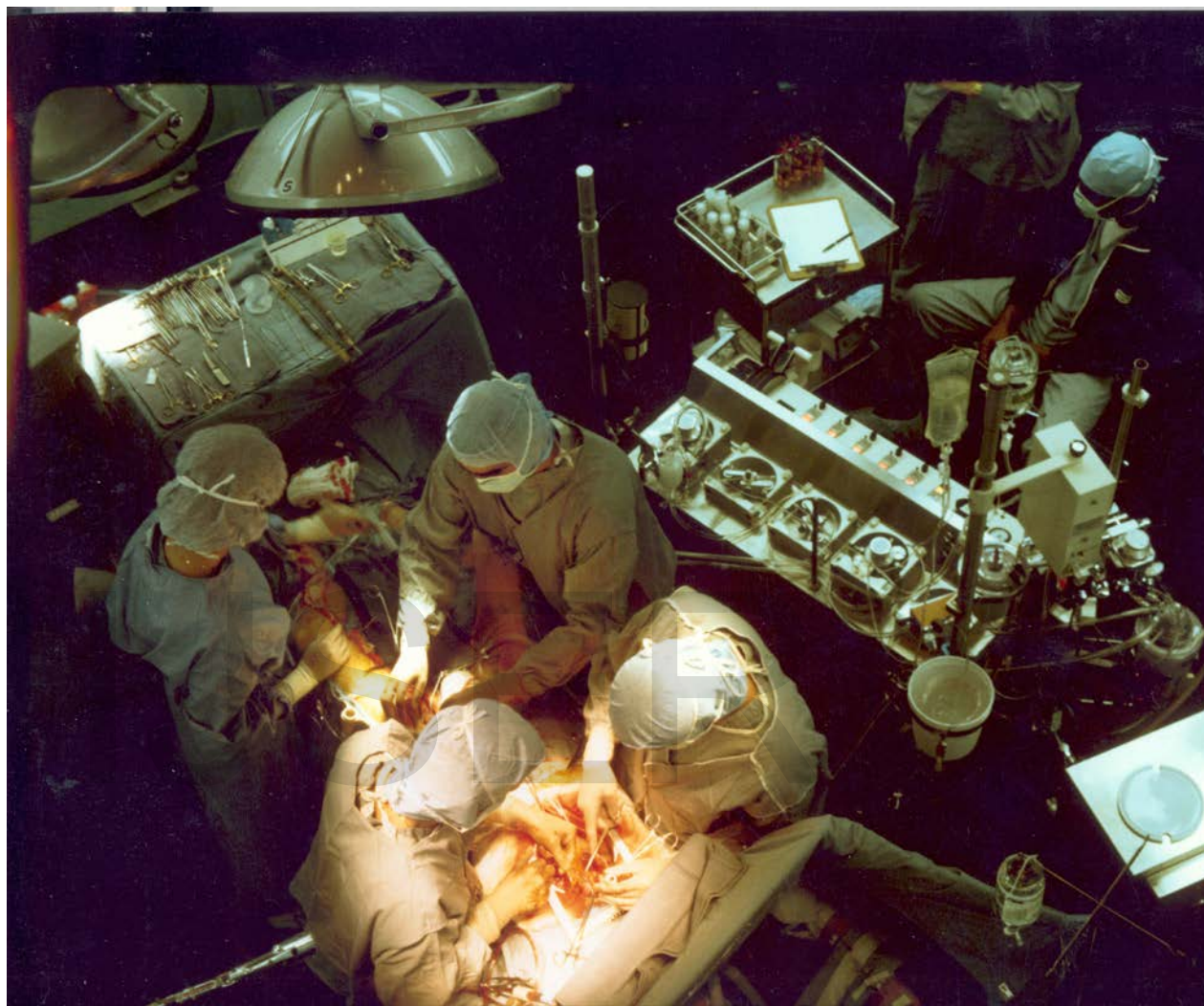


Fig 1.1
Conventional On-pump Coronary Artery Bypass Grafting (CABG) underway.

The association of possible visceral ischemia, renal hypo perfusion, post clamp myocardial dysfunction & prolonged ICU stay have had been well enumerated in the recent and past endeavours to determine the on-CPB perioperative hypo-perfusion as one of the culprits but to date it could not be confidently beleaguered and addressed as the precise causal-effect perpetrator.^{9,10,11,12}

The current study included all the possible variables / multi-system / viscera possibly affected by systemic hypo-perfusion perioperatively on CPB like Cerebral /Neurological dysfunction, Perioperative MI, Low CO, Renal Dysfunction, Prolonged ventilatory dependence and ICU stay, all inclusive.^{2,7,13,14,15}

The close proximated interaction of Temperature with Perfusion –Pressures and on-CPB flows and its effect on perfusion pressure –requirements of end organs like Kidneys and Brain was adequately tackled by monotonous routine of our surgical team to carry out all elective and emergency coronaries at mild hypothermia by drifting at / around 32 degree Celcius (C) and maintaining pump-Flows on average at 2-4L / min based on body surface area (BSA).^{16,6}

2. Materials & Methods

It was a prospective study carried out over a period of 3 years, between Mar, 2014---Feb, 2017. Total No. of 467 patients in all were followed at Tahir Heart Institute, Chinniot Faisalabad Pakistan. Very few patients amongst these were included from other private hospitals of our surgical team's Practice Avenues including Quaid-e-Azam Hospital & Bahria Phase -8 Hospital Cardiac Units Rawalpindi, Pakistan. All Patients undergoing CABG were randomly assorted to both groups. Group I ($n_1=260$) were allocated to Higher perfusion (HP) pressures on-CPB (HP Group). Group II ($n_2=207$) entailed Lower perfusion (LP) pressure – patients on-pump perioperatively. HP was defined as $>75\text{mmHg}$ & LP was defined as $<70\text{mmHg}$ (60-69mmHg). Renal Dysfunction was defined as any Renal profile/ derangement befalling in criterion of RIFLE (Risk Injury Failure Loss & End stage kidney disease classification system) Stage 2-3 or beyond.¹⁷

Preoperative Neurological assessment entailed complete History and physical neurovascular & carotid examination as well as Carotid Doppler studies for all those indicated like (Left Main Stem (LMS), LM Equivalent, PVD (Peripheral Vascular Disease), Diabetics, Positive carotid Bruits, Age >60 yrs & Significant past neurological history). Besides Pre-Op CT Scan Brain for patients with past CVA /stroke was routinely performed.

Bed side Mini-Mental State Examination (MMSE) was ubiquitously conducted on all patients both pre- & post - operatively for neurological and cognitive assessment. Patients (Pts.) with gross infarcts / CVA / Past Stroke and Pre-Op Cognitive decline were excluded from the study. CVA / stroke were defined as cerebrovascular / neurological injury/deficit with gross manifestations clinically or with documented evidence on CT/ MRI.

Post-Op Cognitive Dysfunction (POCD) was defined as below 70th percentile on MMSE and Cognitive & Personality Testing. Exclusion criteria included Pre-op CVA/ stroke, cognitive dysfunction, pre-op renal dysfunction, grade -4/5 Aortic (Ao) atherosclerotic disease, and severe debilitating Chronic Obstructive Pulmonary Disease /COPD (Only mild-moderate COPD pts with pulmonary function tests / PFTs $>60\%$ and $\text{PaO}_2 >65\%$ on room air and / OR stable either on mobile supplemental oxygen or inhaled steroids and with no signs of acute distress, ARDS (acute respiratory distress syndrome) or Type I & II Respiratory Failure were allowed to be included in study). Similarly generalized PVD pts were also included along with very few carotid disease & grade 1-2 Ao disease Pts. PVD was graded and labelled on clinical vascular examination & imaging studies, whereas carotid disease was only labelled for those pts with significant carotid stenosis $>75\%$ well documented on Carotid Doppler or Angiography.

All CABG were done via conventional median sternotomy incisions with Ao & 2 stage atrial cannulation and conventional on – CPB with standard full dose Heparinization. CABG performed on fully arrested heart with tepid blood cardioplegia and systemic hypothermia at 32°C . All cases were done on biocompatible circuits with membrane oxygenators and micro – bubble filters. Standard Ascending Aortic (AAo) cannulation with curved Ao Cannulas (selected according to BSA & Flow requirements on pump) was routinely performed for all cases in the study.

Pre-op characteristics of patients belonging to both the groups are mentioned in table below. Refer to (Table 2.1)

Prolonged ICU stay was defined as cardiac ICU (CICU) stay >7 days. Although included later as secondary outcome in study, any In-hospital death (perioperative / post - operative) within 1 yr post surgery due to cardiac related issue was taken as Mortality. Prolonged ventilatory dependence was defined as >5 days in CICU. All the collected data & comparison between two groups were computed and analyzed with SPSS 16.0 & the results were tabulated and depicted graphically.

Low cardiac output (CO) was defined as inability to maintain systemic perfusion pressures along with visual and echocardiographic evidence of ventricular dysfunction post – CPB in previously normal pre-op LV Ejection Fraction (EF) leading either to resolution after a brief period of resumption of CPB or entailing IABP dependence / requirement. IABP dependence was labelled only to those Low CO pts with prior normal LVEF, which do not improve even after a considerable period of LV off-loading on bypass despite maximal inotropic and lusitropic support. Periop MI (Myocardial Infarction)

was defined as persistent raised cardiac enzymes (CK-MB) up to 5 times the 99th percentile of normal levels besides electrocardiographic and echocardiographic standard evidence.

Variables	Higher Perfusion / HP (56%) n1= 260	Lower Perfusion / LP (44%) n2 =207	p-Value
Age >70	26 (10%)	4 (2%)	0.03
<70 (60-69)	130 (50%)	99 (48%)	0.07
<60	104 (40%)	104 (50%)	0.06
Male (65%)	55%	45%	0.07
Female (35%)	43%	57%	0.06
NYHA class I-II (92%)	60%	40%	0.08
3VCAD/ (55%)	27%	28%	0.09
1-2VCAD (5%)	4.5%	0.5%	0.04
LMS (17%)	10%	7%	0.07
LM Equivalent (18%)	9%	9%	0.08
(All with Fair / Good LV)			
Afib (5%)	2 %	3%	0.06
Peripheral Vascular Disease (PVD) (12%)	5%	7%	0.07
/Carotid Disease (7%)	3%	4%	0.08
/ Grade 4- Ao Disease	--NIL--	--NIL--	----
Preop renal dysfunction	--NIL--	--NIL--	----
DM (70%)	75%	25%	0.03
HTN (41%)	65%	35%	0.04
EF <35% --- Preop IABP (8%)	04%	04%	0.08
COPD (3%)	1.5%	1.5%	0.09
Previous stroke	--NIL--	--NIL--	----
Previous Cognitive dysfunction	--NIL	--NIL--	----

Table 2.1
Preoperative Patient Population Characteristics

3. Results

Total Patients (N=467) were operated for 3VCAD (55%), 1-2VCAD (5%), Left Main Stem (LMS 17%), LM Equivalent (18%); most of them (92%) were with Fair LV and presented with New York Heart Association (NYHA) class I/ II. Very few amongst them (8%) had low EF (<35 %) & NYHA Class III/IV symptoms.

Patient population randomly distributed into two groups; one underwent higher perfusion (HP /n₁ = 260) on – pump (56% of total population N = 467) & the second underwent lower perfusion (LP

$n_2 = 207$) on – CPB (44% of $N = 467$) .Two populations (n_1 & n_2) were uniformly matched for all variables / pre - op patient characteristics to avoid untoward confounding bias.

Disease pattern was also matched with equality in 2 populations except statistically significant difference in distribution of 1-2 VCAD patients ($p < 0.05$) with higher percentage of these pts in HP group, though 1-2 VCAD pts represented very little proportion (5%) of total (N) number of patients.

Similarly Diabetic, Hypertensive and Old Aged > 70 yrs also got randomly distributed at statistically significant higher proportion in HP group ($p < 0.05$). Refer to Table 2.1 for Pre-op Pt population characteristics.

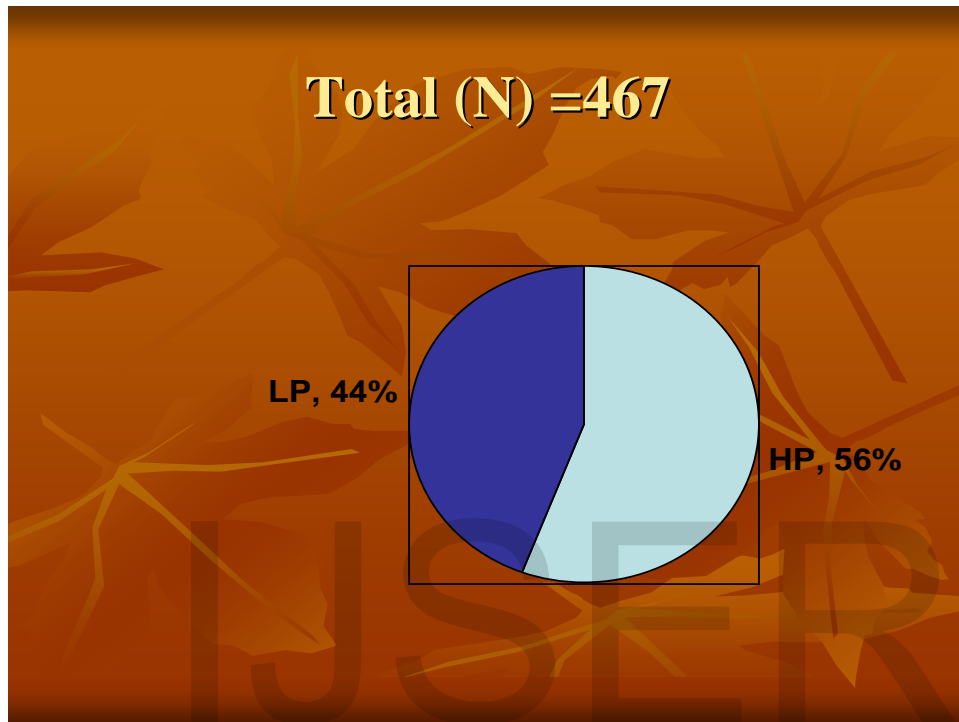


Fig 3.1 Sample Distribution

HP (n_1) = Higher Perfusion Gp

LP (n_2) = Lower Perfusion Gp

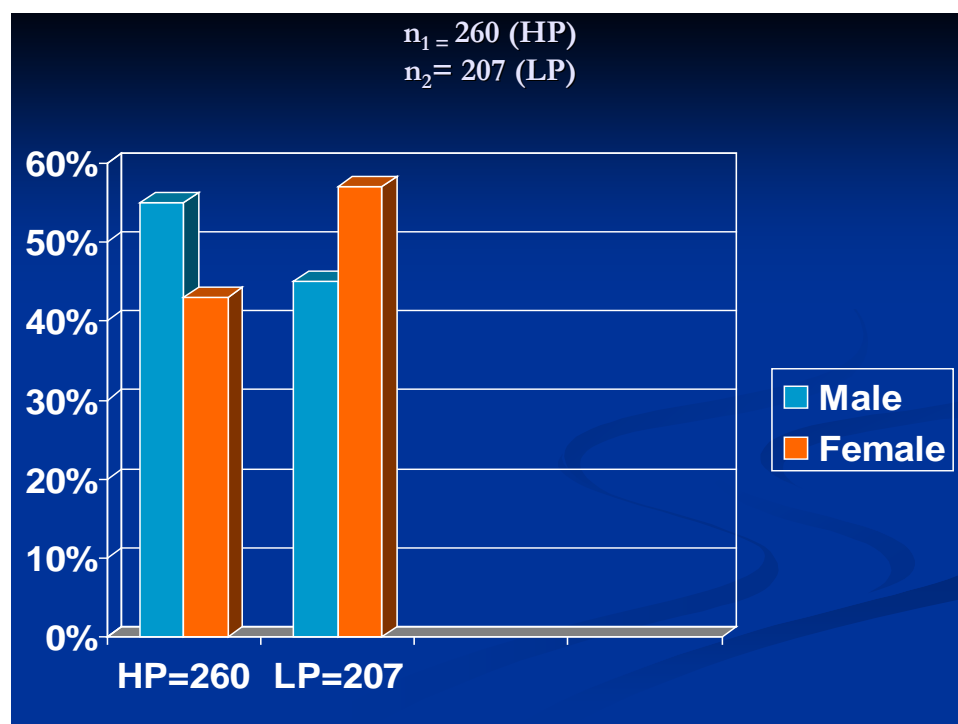


Fig 3.2 **Gender Distribution**

So overall two properly matched cohorts were compared for variables like Renal Dysfunction (RD), prolonged ventilation, POCD, Stroke /CVA , prolonged CICU stay as Primary outcomes of the study & the results were computed and analyzed by SPSS 16.0 & tabulated and graphically represented (as Table 3.3 and Fig. 3.1-----3.10) .The secondary outcomes were followed in the study as Periop MI, Low CO, Mortality & IABP dependence.

<u>Variables</u>	<u>HP Group/ n₁</u> 56% / 260 (N = 467)	<u>LP Group/ n₂</u> 44% / 207 (N = 467)	<u>p-value</u>
POCD	0.41% / (1)	3.8% / (8)	0.03
Renal Dysfunction	1.5% / (4)	4% / (8)	0.04
Stroke/ CVA	0.4 % / (1)	0.5% / (1)	0.09
ICU stay > 7 Days	1.28% / (3)	4.9% / (10)	0.02
Ventilation > 7Day	0.9 % / (2)	1.5% / (3)	0.056
Periop MI	3.5% / (9)	3.2% / (6)	0.05

Low CO	2.5% / (6)	5.7% / (12)	0.04			
IABP Dependency	4.8% / (13)	2.9% / (6)	0.045			
Mortality	1.5% / (4)	3% / (6)	0.05			

Table 3.3
RESULTS

Overall results construed with statistically significant ($p < 0.05$) better outcomes in HP group in terms of ICU stay, RD (renal dysfunction) & POCD (post operative cognitive dysfunction). Borderline statistical significance was observed among variables like prolong Ventilation, Peri-op MI & Mortality whereas Low CO was significantly lower in HP group in contrast to IABP- requirement / Dependence which was witnessed far greater in HP cohort as compared to LP ($p < 0.05$).

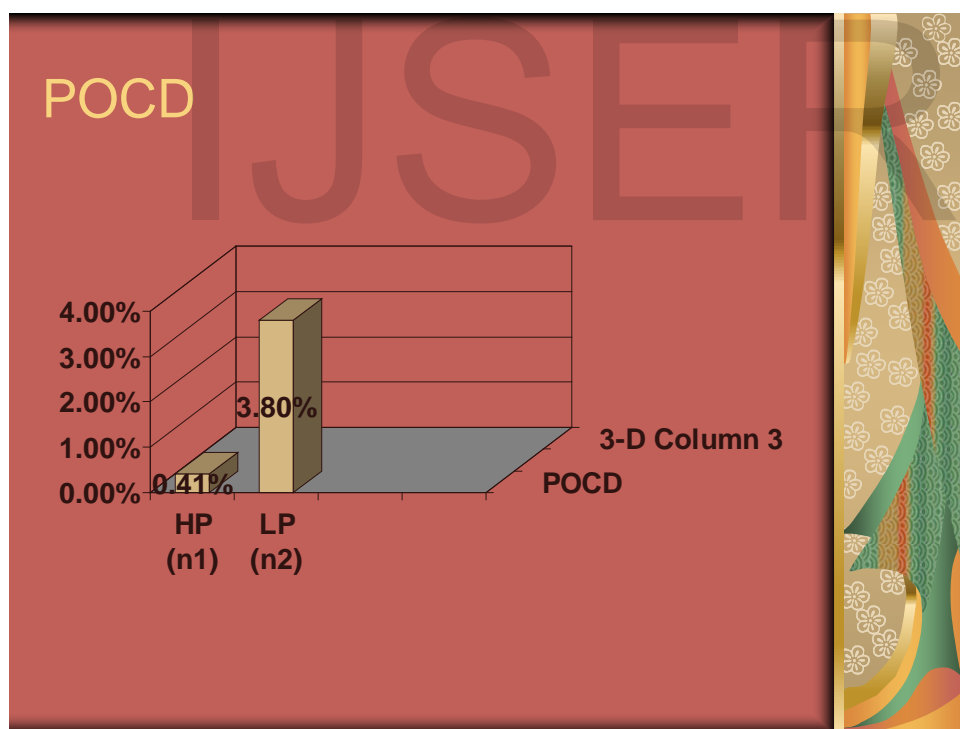


Fig 3.4
Post Op Cognitive Dysfunction (POCD) - Comparison in 2 Groups

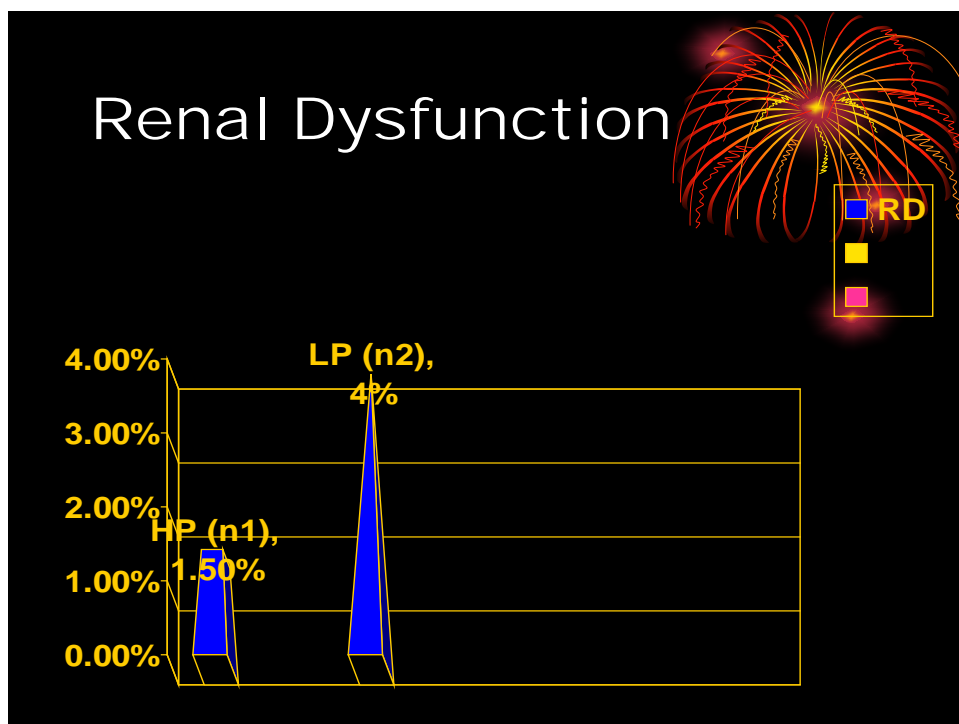


Fig 3.5
Comparison RD (Renal Dysfunction) in HP & LP groups.

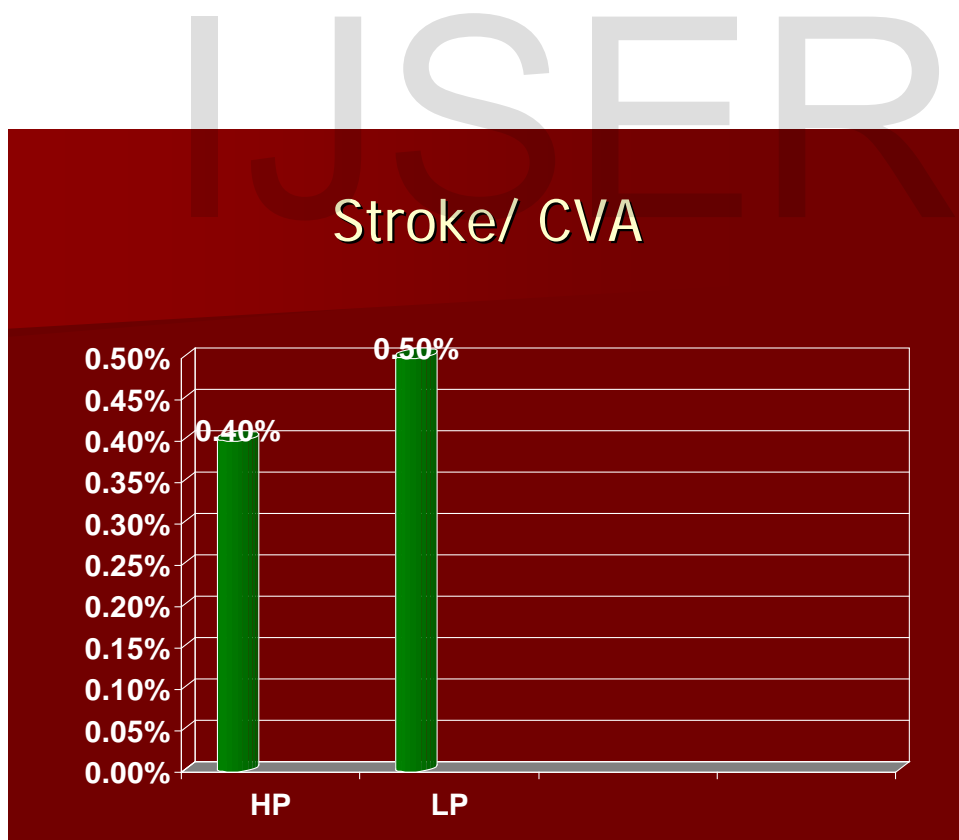


Fig 3.6

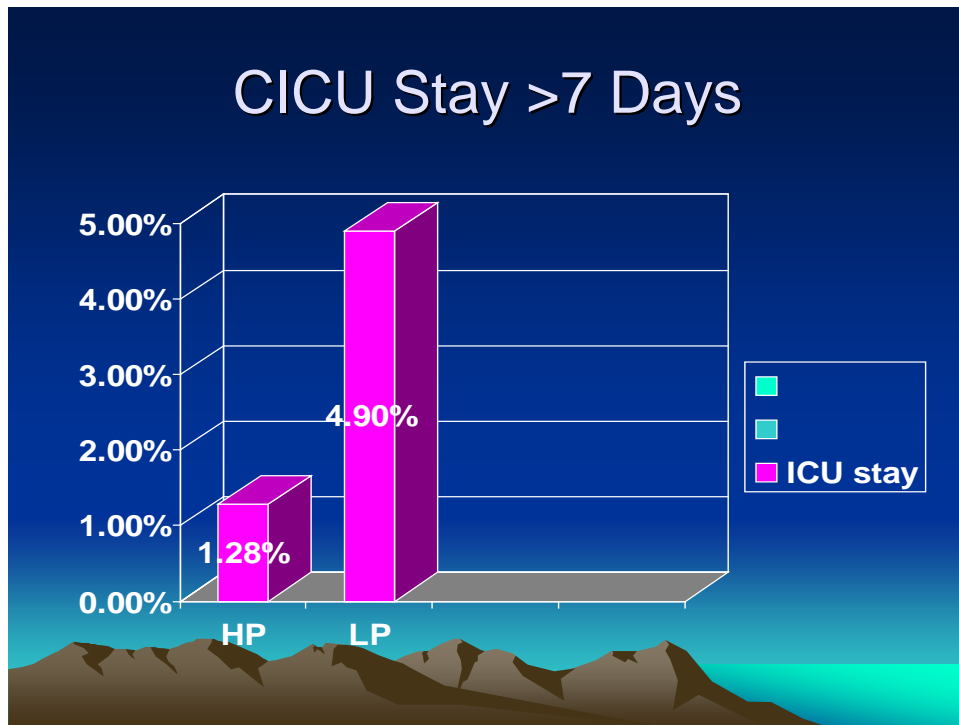


Fig 3.7

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Ventilation > 7 days

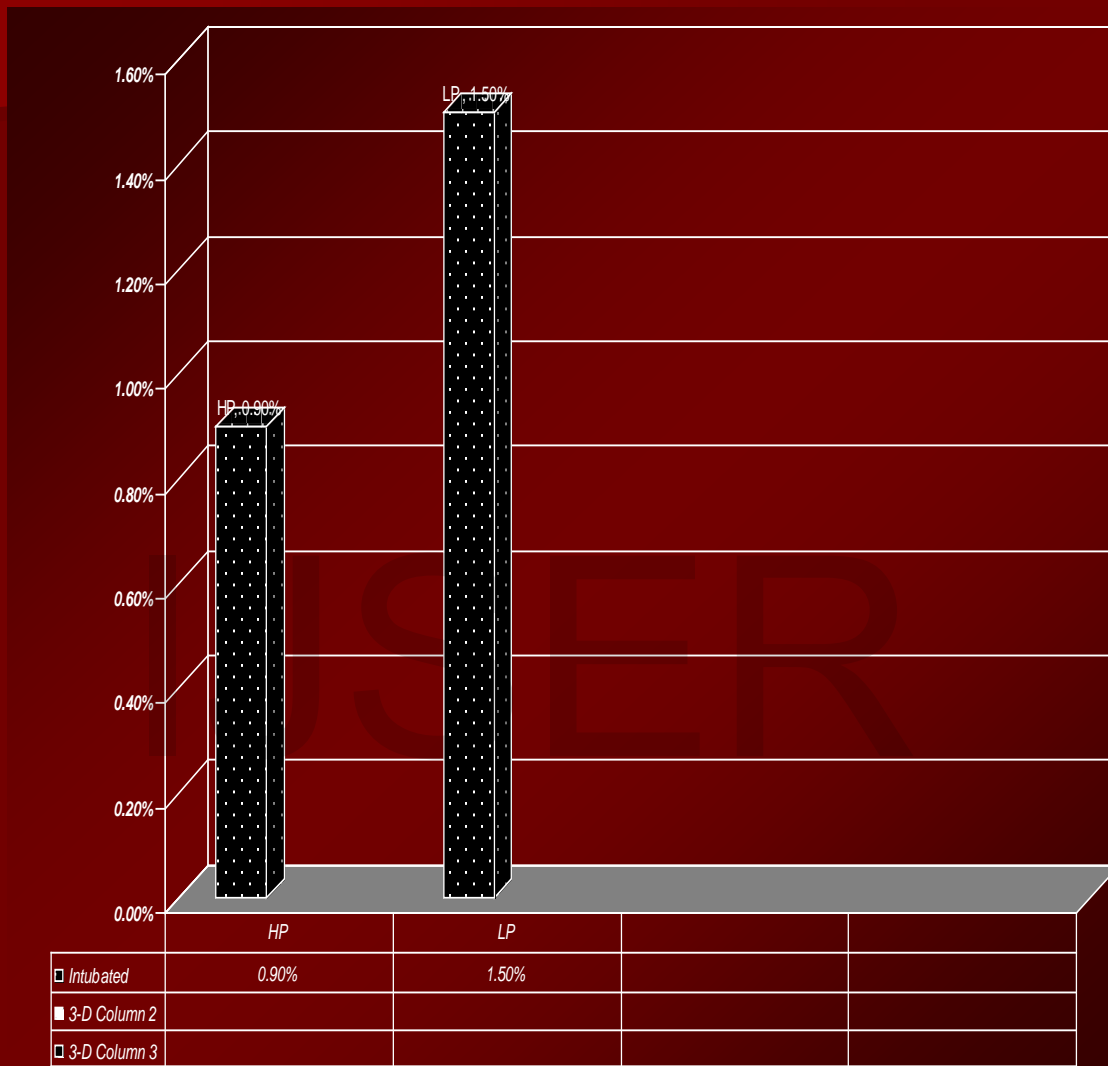


Fig 3.8
Prolonged Ventilation Comparison Amongst the Two Groups

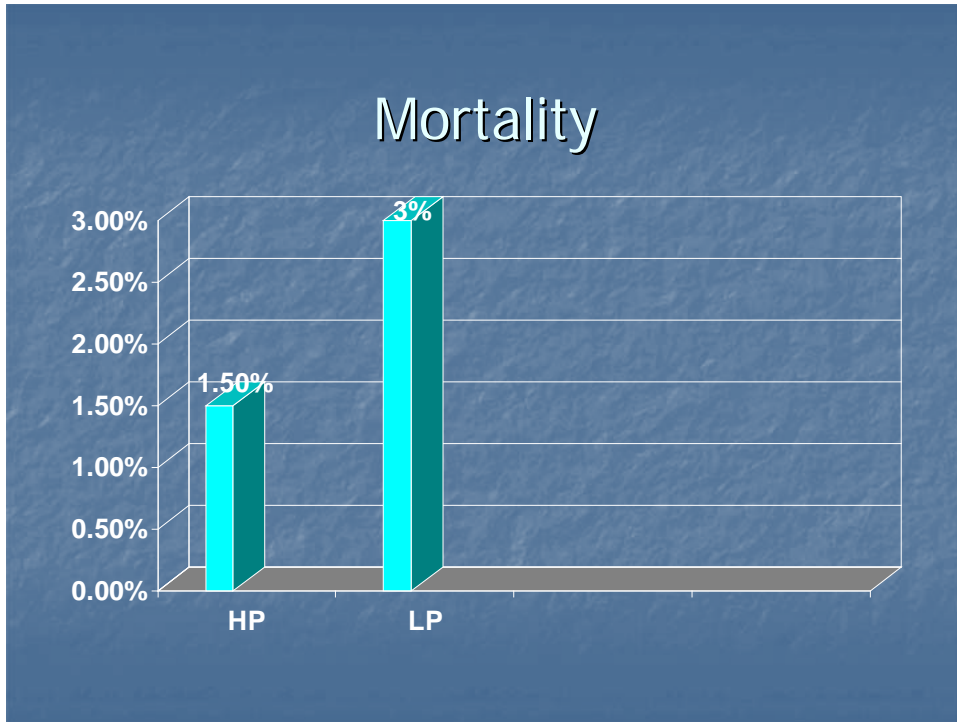


Fig 3.9

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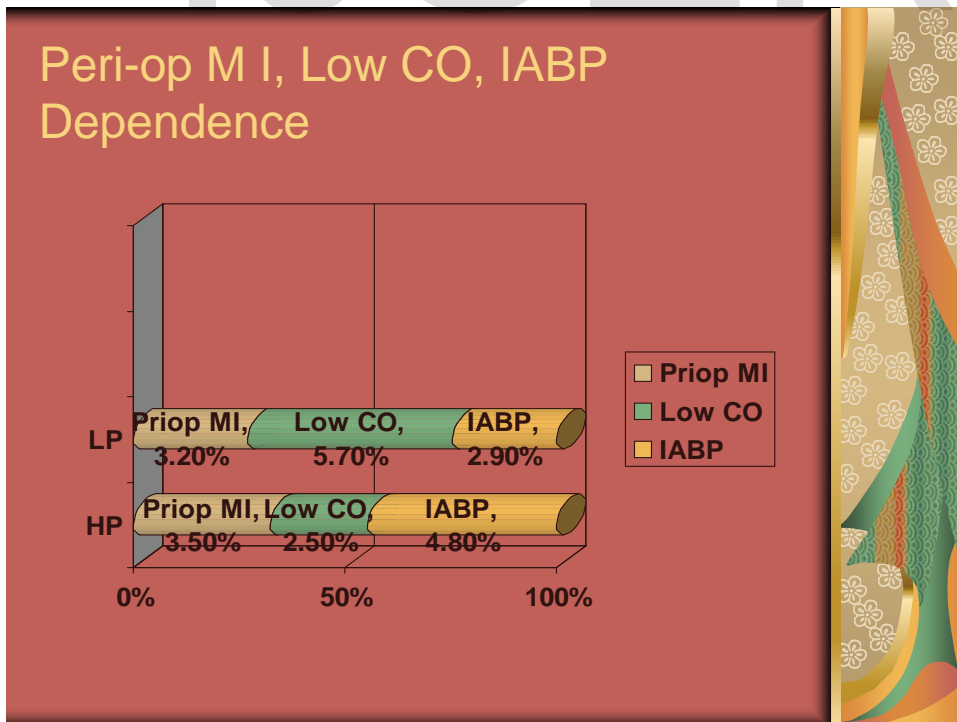


Fig 3.10

4. **Discussion:**

Ever since the inception of coronary artery bypass grafting (CABG), it has had been a treatment modality for ischemic heart disease (IHD) patients presenting as a myriad of clinical continuum vocalized as chronic stable angina (unresponsive to maximal medical therapy or not feasible for available coronary cath interventions in different eras), acute coronary syndromes (ACS) encompassing Non – ST elevated MI (NSTEMI) with either stable angina or on going ischemia & ST – elevated MI (STEMI) with failed or non – feasible percutaneous coronary interventions (PCI) or as life threatening emergent CABG for mechanical complications of IHD. CABG as mode of definitive treatment strategy has so far been immensely successful not only as medical salvage, but also as objective alleviator of symptoms & as a hallmark of improved Quality of Life (QOL) and well documented & unanimously accepted precursor of social, physical and mental rehabilitation of a cardiac patient (Pt.)¹⁸

Despite impeccable advances in coronary surgery embarked upon by glorious & seducing Robotic choices (like Totally endoscopic coronary artery bypass /TECAB) as well as Minimally invasive procedures like MIDCAB (Minimally Invasive Direct Coronary Artery Bypass) and endoscopic – coronary options like EndoACAB (Endoscopic Atraumatic Coronary Artery Bypass) & much debated OPCAB (Off pump CABG) and on-pump traditional choices, conventional on -bypass CABG remains the most widely practiced and allured choice of surgeons all over the world today.¹⁹

On – pump satisfactory perfusion pressures and their natural impact on vital organs – salvage has always been the prime concern of cardiac surgeons perioperatively well communicated and handled by Troika in the form of Surgeon, Anaesthesiologist and Perfusionist. Continuum of accepted range of perfusion pressures have been the consensus universally over the last four decades specifically. Lower Perfusion (LP) pressures below the accepted range can deliver devitalizing injuries to precious targets like central nervous system (CNS), cardiovascular system (CVS) as well as Splanchnic & Renal perfusion systems. Higher Perfusion pressures even beyond the traditional unanimously practiced perfusion –pressures range have had recently been deciphered for pts with co-morbidities like HTN, Renal dysfunction, CVA & past neurological history.²⁰

Neurological impact related to Hypo - Perfusion hits perioperatively is mostly cited as Type II neurological dysfunction including delirium, arithmetic and cognitive dysfunction (POCD) & personality changes postoperatively in contemporary data. Overall hypothetical hypo- perfusional ischemic insult can affect cardiovascular, respiratory, renal, splanchnic systems & vital abdominal viscera besides Heart and Brain. The current study is the humble endeavour to delineate the positive impact of well purported Higher Perfusion (HP) pressures (> 75mmHg) under all conditions, on over all safety, survival and morbidity of patients undergoing on – pump conventional CABG as an index of perioperative superior preservation of vital systems. However as an element of saneness and safety, the comparison cohort was not thrown across unsafe range of unanimously unaccepted perfusion range of pressures (< 50mmHg), rather the comparison continuum of Lower Perfusion (LP) in (n₂) cohort was established as a higher percentile range of LP - pressures (i.e. between 60---69mmHg) so that perfusion pressures were never allowed to fall below 60 mmHg.^{21, 22, 23}

The two cohorts were randomly distributed across the total pt. population (N =467) yet were maximally uniformly matched for all preoperative possible confounding factors, pre - op patient characteristics and variables but certain factors like DM & HTN could not be controlled or were overlooked being got randomly assorted in significantly higher proportions to one group (HP/ n₁), though it were allowed to persist as such to look at it as possible independent association of diabetics and hypertensive patients having beneficial impact of Higher perfusion – pressures perioperatively. Similarly very elderly (>70 yr old) pts were intentionally allocated to HP cohort as an intentional ethical bias (on - lookers bias / Hawthorne effect) with minimal to almost none in LP group but the overall percentage /proportion of elderly strata among the total (N) population was statistically not significant enough to influence the overall course of study & impact on final results.

Another important confounding factor in this study as 1-2 VCAD pts noticed as being significantly higher in HP group could possibly benefit that cohort hypothetically in comparison with LP cohort in terms of possible better & less morbid disease pattern being allocated to HP and could confound the independent comparison between 2 Groups but again the overall proportion of these patients in HP Group as well as in total (N) population did not have statistical power to influence the

results or create a confounding impact. Besides none of these single / double vessel disease was straight forward simple non- LAD territory - type piece of cakes; rather almost all of them were referred for surgery either because of critical proximal stenosis of LMS / LAD / LM equivalent vessels or because of diffusely diseased vessels not amenable to simple PCI. So if at all they had any minimal impact, that could have been against the alternate hypothesis of our study entailing HP –pressures as favourable entity for overall morbidity of pts undergoing conventional on – bypass CABG.

Overall Results were computed and analyzed by SPSS 16.0 & were favourable for HP pressures on- pump perioperatively for pts undergoing CABG in terms of less POCD, Renal Dysfunction (labelled as RIFLE stage 2-3) & CICU stay in statistically significant range ($p < 0.05$). Refer to Table 3.3 & Fig 3.4, 3.5 & 3.7. All of them were the primary outcomes of this study. POCD was noted in 0.41% ($n = 1$) of HP / n_1 population (1/260) and 3.8% ($n=8$) of LP / n_2 population (8/ 207). RIFLE stage 2-3 or beyond was witnessed as 1.5% ($n=1$) of HP ($n_1 = 260$) whereas it was significantly ($p < 0.05$) higher proportion (4%) of total LP group ($n_2 = 207$) population. Prolonged CICU stay was significantly higher (4.9% , $n = 10/207$) in LP cohort whereas it was just 1.28% ($n = 3/260$) in HP. Stroke, albeit was observed slightly more in LP as compared to HP cohort but was not statistically significant. (Fig 3.6 & Table 3.3). The secondary outcomes in this study were Mortality, Prolonged ventilation, Periop MI, Low CO & IABP –Dependence.

The interesting data was gathered regarding Mortality; although proportionately very high percentage mortality was seen in LP group, it never touched statistical significance; rather it was a case of border line significance along with others like Periop MI & prolonged ventilation. (See Fig 3.8, 3.9, 3.10 & table 3.3). The ambivalence showered around hypothetically contradicting data related to Low CO & IABP- dependence in a way that Low CO was more significantly prominent in LP as compared to HP group & IABP –requirement was more prevalently observed significantly ($p < 0.05$) in HP cohort. The apparently contradicting results couldn't have been disregarded because of their statistical significance. The rationally construed approach was adopted. The Low CO in LP cohort was attributed to poor myocardial preservation perioperatively in post - Ao clamp period seemingly due to lower perfusing pressures.

Similarly IABP – dependence (which was operationally defined as IABP requirement in previously normal LVEF pts despite maximal medical, inotropic & lusitropic support and Low CO not improving even after a considerable period of LV off – loading on CPB) which was witnessed significantly higher in HP group, could possibly be attributed to higher Afterloads subjected to struggling LV (which probably had some periop insult before hand) by higher perfusion pressures & higher systemic vascular resistance (SVR) further stimulating the idea regarding beneficial effects of higher Flows rather than higher Perfusion pressures peri-operatively.^{24, 25}

Overall Study concluded in favour of HP – pressures for CABG pts on-pump perioperatively in terms of overall morbidity especially in terms of our primary outcomes like Renal function, POCD & ICU stay besides illuminating interesting foci & thought provoking data regarding secondary outcomes of this study. There was no conflict of interest and apparently neither was any limitation.

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