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Original Article

“Assessing the hemodynamic impact of various inotropes combination in patients with cardiogenic shock with Non-ST elevation myocardial infarction –the ANAPHOR study”



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ABSTRACT

Background: Various inotropic agents/vasopressors combinations are used in patients of cardiogenic shock. We performed this study to observe hemodynamic effects of various inotrope/vasopressor combinations in patients with NSTEMI cardiogenic shock (CS) at tertiary cardiac centre

Methods and materials: Of 3832 NSTEMI, we studied 59 consecutive such patients with CS who hadn't undergone revascularization in the first 24 h in a prospective, open label, observational study. Group 1 comprised of background Dopamine with Noradrenaline titration(N = 38), Group 2 had background Dobutamine and Noradrenaline titration(N = 15) and Group 3 comprised of triple combination of Dopamine, Noradrenaline & Adrenaline(N = 6).

Results: The mean change in hemodynamic parameters between these groups from baseline to 24 h showed no statistical difference. Cardiac output(CO), mean arterial pressure(MAP), central venous pressure(CVP) and cardiac power output(CPO) in group 2 were favorable at 6 and 24 h compared to baseline but mean change was insignificant as compared to others. In group 3, the increase in MAP was significant. IABP use did not change CO, CPO or SVR in any group except lower dosages of Dobutamine (49%) in IABP group. Lower in-hospital mortality in group 2 compared to others (P = 0.004) may be reflective of sicker patients in group 1 and 3.

Conclusion: The mean changes in hemodynamic parameters were not significant between all groups. All regimes of inotropes when selected as per clinical indication in CS with ACS resulted in similar hemodynamic effects. The mortality difference may not truly be reflective of regimes rather reflect sicker patients in the higher mortality group.

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1. Introduction

Cardiogenic shock (CS) is a low cardiac output (CO) state due to heart failure, resulting in life-threatening end-organ hypoperfusion and hypoxia.¹ It is associated with high mortality. The incidence of cardiogenic shock is approximately 7% (5%–8%) in ST-elevation myocardial infarction and 2.5% in non-ST elevation myocardial infarction patients.² Shock results in impaired tissue perfusion, cellular hypoxia, and metabolic derangements that cause cellular injury. Although this early injury is often reversible, persistent hypoperfusion leads to irreversible tissue damage, progressive organ dysfunction and can progress to death.³

Hemodynamic instability is a common cause of morbidity and mortality in cardiac patients. In clinical practice, hemodynamic instability is routinely defined as a systolic blood pressure <90 mm Hg.⁴ However, when considering hemodynamic instability, clinicians should be more concerned with organ hypoperfusion rather than only on blood pressure. In most patients with hemodynamic instability, administration of intravenous fluids is initially used as an attempt to improve hemodynamics. Typical signs of shock include low blood pressure, rapid heart rate and poor organ perfusion as indicated by low urine output, confusion or loss of consciousness. After fluid resuscitation, vasopressors/inotropes are the main stay of treatment apart from Mechanical support devices. Inotropes and vasopressors increase myocardial contractility and modify vascular tone through the activation of adrenergic pathways. The effect varies depending on the interaction with the various receptors in the myocardium and the vascular smooth muscle.² Descriptions of the use of inotropes and vasopressors in Shock go back to the 1950s,^{5,6} but there have been very few clinical trials in these patients and so the choice of which drug combination to be used in this setting remains unclear.

We have tried studying the effects of commonly used inotropes and vasopressors combinations on Cardiac Output (CO), Central Venous Pressure (CVP), Cardiac Power output (CPO) and SVR (Systemic vascular resistance) apart from its effect on in hospital mortality.

2. Materials and methods

Out of 3832 patients presenting with NSTEMI, we studied in a prospective observational study of 59 consecutive patients who presented with NSTEMI with cardiogenic shock (CS) and did not undergo revascularization within first 24 h at the tertiary care Cardiology Centre between November 2016 to January 2019. The study was approved by institutional ethics committee (UNMICRC/CARDIO/2016/16) as per the Helsinki Declaration of 1975, as revised in 2000. Informed written consent was obtained from all patients/attendants as per protocol prior to enrollment into the study.

The inclusion criteria were presence of cardiogenic shock (as per the definition of shock used in IABP-SHOCK II trial)⁷ in patients with NSTEMI if they had a systolic blood pressure of less than 90 mm Hg for more than 30 min or needed infusion of catecholamine to maintain a systolic pressure above 90 mm Hg, had clinical signs of pulmonary congestion, and had impaired end-organ perfusion. The diagnosis of impaired end-organ perfusion required at least one of the following: altered mental status; cold, clammy skin and extremities; oliguria with urine output of less than 30 ml per hour; or serum lactate level higher than 2.0 mmol/L. Exclusion criteria of the patients were any of the following - if they were younger than 18 years or had already received a vasopressor (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 h during the current episode of shock or were on any cardiac medication prior like beta-blockers, calcium channel blockers or any previous cardiac medications or had a serious arrhythmia such as rapid atrial

fibrillation (>160 beats per minute) or ventricular tachycardia and patient who was planned or already on ECMO/Impella or other mechanical circulatory devices apart from IABP. All patients who underwent coronary angiography (with intent to revascularization) within 24 h were also excluded to negate the impact of revascularization on hemodynamics. Patients of CS with STEMI were excluded because the various guidelines recommend earliest revascularization for them and it would have been unethical to have that arm in the study. However, in 2016 when the study was designed, the early vs delayed invasive strategy was still being evaluated world-over and hence the same was allowed by ethical committee based on the prevalent studies and guidelines for only those who didn't undergo revascularization within 24 h of hospitalization.^{8,9}

All the patients underwent routine investigations on presentation which included ECG, 2D Echocardiography, Chest X-ray, Complete blood count, renal and liver function tests, S. Lactate levels and Cardiac biomarkers of ACS. All Hemodynamic parameters viz CO, SVR, MAP, CPO and CVP were recorded at the baseline time point of presentation, at 6 h and again at 24 h. MAP (Mean arterial pressure) was measured by using the formula- Diastolic Blood Pressure (DBP) + 1/3 Pulse pressure. Central venous pressure (CVP) line was placed to measure the same. Cardiac output was calculated at baseline using Fick's principle. Oxygen consumption was estimated using Lafarge et al normograms based on age, gender and heart rate.¹⁰ CO was measured "invasively" using Fick's principle with invasive pressures and oxygen saturations being measured for the right heart using Swan-Ganz catheter by the bedside and the left sided pressures and saturations being measured using femoral/radial arterial lines. It was measured using the thermodilution techniques. CO thus calculated at baseline, also yielded Cardiac Index at the baseline. The cardiac power output (CPO) was calculated using formula $CPO = MAP \times CO / 451$.

Based on the baseline assessment of MAP, CO, CI, CPO and SVR, inotropes and vasopressors were started for treatment of shock after calculating dosage per body weight as per the standard management protocols to treat cardiogenic shock with titration of vasopressors/inotropes left to the discretion of the treating intensivist and consultant to achieve the hemodynamic goals. The various inotropes and vasopressors used were Dopamine, Noradrenalin, Adrenalin, and Dobutamine. Based on CO, CI, CP and SVR calculated at 6 h, dosage of Inotropes and vasopressors were modified, and continued till 24 h or beyond as warranted.

3. Statistical analysis

All statistical analysis was performed using SPSS v 20.0 (Chicago, IL, USA). Continuous variables were compared using the unpaired student's *t*-test or one-way analysis of variance (ANOVA). Continuous variables were summarized as mean ± standard deviation (SD) whereas categorical variables were expressed as percentage of the sample. Regression analysis was done to find out the difference in cardiac output, SVR, CI and CPO. Group differences associated with a *p* value ≤ 0.05 were considered statistically significant. The inter-group data were analysed and same has been reported. The intra-group comparisons are only for the significant variables.

4. Results

There was no significant difference amongst baseline risk factors like smoking (*P* = 0.17), hypertension (*P* = 0.97), Diabetes mellitus-II (*P* = 0.49), LVEF (*P* = 0.42) on admission between these groups shown in Table 1. The baseline characteristics were matched between 3 groups and only the significant parameters are mentioned in the manuscript.

Mean age of population was 56.8 ± 13.23 years with majority being males (73.3%). Mean delay in presentation from the onset of symptoms in group 1, group 2 and group 3 were 221 ± 28 min, 199 ± 48 min and 249 ± 56 min respectively and the same were statistically not significant ($P = 0.2$). Majority of the patients were on dual inotropes/vasopressors which have been analyzed into these 3 groups. Group:1 had background dopamine and noradrenaline titration in 38(63.3%) patients, Group:2 had background Dobutamine and Noradrenaline in 15(25%) patients, and Group:3 had Dopamine, Noradrenaline & Adrenaline in 6(10%) patients. The mean change in hemodynamic parameters was calculated from those measured at baseline, at 6 h and at 24 h. In Group 1 the mean dopamine starting baseline dose was 14.37mcg/kg/min and that of noradrenaline was 8.74mcg/min. The mean CO (3.05 ± 0.51 , 3.39 ± 0.59 and 3.76 ± 0.54 l/min; $P < 0.0001$), SVR (1369.76 ± 238.99 , 1466.08 ± 240.44 and 1460.50 ± 165.98 dyne/cm⁻⁵/m²; $P = 0.1$), CI (1.82 ± 0.39 , 2.13 ± 1.02 and 2.03 ± 0.16 L/min/m²; $P = 0.09$), MAP (62.76 ± 6.21 , 69.61 ± 5.49 and 74.42 ± 4.95 mmHg; $P < 0.0001$), CVP (13.71 ± 9.79 , 11.58 ± 10.54 , 10.29 ± 11.72 cm; $P = 0.38$) and CPO (0.42 ± 0.08 , 0.52 ± 0.10 and 0.62 ± 0.10 W; $P < 0.0001$) were calculated at baseline, 6 and 24 h respectively. There was a significant change in CO and MAP and CPO over 24 h with titration of doses of Noradrenaline. There was no significant change seen in Dopamine dosage changes ($P = 0.47$) as compared to significant change of noradrenaline dose only in group 1.

Group 2 showed the combination of background dobutamine and noradrenaline titration with the baseline dose of 6.13 mcg/kg/min and 8.20 mcg/min. respectively. The mean CO (2.87 ± 0.35 , 3.40 ± 0.51 and 3.53 ± 0.52 l/min; $P = 0.001$), SVR (1452.2 ± 128.79 , 1499.0 ± 160.91 and 1555.4 ± 178.46 dyne/cm⁻⁵/m²; $P = 0.21$), CI (1.8 ± 0.41 , 1.87 ± 0.35 and 2.0 ± 0.0 L/min/m²; $P = 0.22$), MAP (64.87 ± 6.06 , 70.8 ± 5.13 and 75.93 ± 3.59 mm Hg; $P < 0.0001$), CVP (11.13 ± 4.57 , 9.20 ± 2.62 and 7.93 ± 1.53 cm; $P = 0.03$) and CPO (0.43 ± 0.08 , 0.53 ± 0.09 and 0.60 ± 0.09 W; $P < 0.0001$) were calculated at baseline, 6 and 24 h respectively. Out of these CO, MAP, CPO and CVP showed a significant change at 24 h as compared to baseline, with the significant up-titration in dosages of Noradrenaline ($P = 0.002$). The mean change in the dosage of dobutamine ($P = 0.63$) was not significantly different from baseline. The SVR did not change significantly with changes in dosages of noradrenaline ($P = 0.21$).

Group 3 showed the combination of dopamine and noradrenaline at the baseline dose of 19.0 mcg/kg/min and 8.67mcg/min respectively and at 6 h mean adrenaline dose was 0.12mcg/kg/min. The mean changes in CO (3.04 ± 0.25 , 3.44 ± 0.39 and 3.59 ± 0.71 l/min; $P = 0.16$), SVR (1344.83 ± 223.19 , 1484.0 ± 184.38 and 1582.0 ± 230.39 dyne/cm⁻⁵/m²; $P = 0.19$), CI (1.76 ± 0.39 , 1.99 ± 0.07 and 2.07 ± 0.29 L/min/m²; $P = 0.02$), MAP (61.0 ± 4.94 , 71.67 ± 3.67 and 77.17 ± 5.81 mm Hg; $P < 0.0001$), CVP (10.33 ± 4.59 , 8.80 ± 2.07 and 7.67 ± 1.37 cm; $P = 0.32$) and CPO (0.41 ± 0.03 , 0.55 ± 0.07 and 0.62 ± 0.15 W; $P = 0.006$) at baseline, 6 and 24 h. The change in CO, CI, SVR, MAP and CPO calculated at 6

and 24 h; CPO and MAP showed a significant change at 24 h compared to that at 6 h but this change did not significantly correlate with changes in the dosages of either Dopamine, Noradrenaline, or adrenaline ($P = 0.99$, 0.39 and 0.17).

The differences between the means of changes in hemodynamic parameters amongst the 3 groups were calculated and it was found that the changes in CO, SVR and, MAP and CI over 24 h were not statistically different as shown in Table 2.

IABP was used in 30 (50.8%) patients with 22(57.9%), 6(40%) and 2(50%) patients in group 1, 2 and 3 respectively and the difference was insignificant ($P = 0.27$) as shown in Table 3. IABP use did not significantly provide any change in CO ($P = 0.79$), CP ($P = 0.31$) or SVR ($P = 0.6$) except lower dosages of dobutamine required in IABP group (4.08 ± 1.41 and 7.92 ± 2.52 ; $P < 0.0001$) as shown in Table 4. Over all, in hospital mortality was 55% in total population (59 patients). Significantly lower in-hospital mortality was seen in group 2 amongst the three groups 65.8%, 20% and 83.3% respectively ($P = 0.004$). This significantly lower mortality need not necessarily suggests that combining baseline dobutamine with Noradrenaline titration was the best strategy amongst the 3 strategies and may be reflective of sicker patients in the higher mortality group. The same can also be inferred from a trend towards lower mean baseline serum lactate levels and Troponin-I in group 2 as compared to group 1 and 3 but was not statistically significant ($P = 0.09, 0.16$) shown in Table 5.

5. Discussion

This study describes the contemporary use of inotrope combinations and its association with in-hospital mortality in CS patients with NSTEMI. It also looks into effects of various inotropes/vasopressors on CO, SVR, CP, and CI. The 2004 ACC/AHA guidelines for ST-elevation myocardial infarction (STEMI) recommended the selection of vasopressor and/or inotrope therapy based on SBP plus the presence or absence of signs and symptoms of shock.¹¹ For patients with an SBP of 70–100 mm Hg, dobutamine was recommended in the absence of shock and dopamine if shock was present. Norepinephrine was recommended when SBP is < 70 mm Hg (Class II) However; the 2013 updated guideline no longer has this algorithm listed.¹²

The current recommendation is individualization of inotropic and vasopressor therapy with invasive hemodynamic monitoring. Noradrenaline is still considered first line for cardiogenic shock. The use of dopamine may have unacceptably high risk.¹² The results of a 2010 multicenter; randomized trial challenged the recommendation of dopamine as a first line vasopressor agent over norepinephrine in cardiogenic shock patients. The trial was conducted to determine if the use of norepinephrine over dopamine as the first line vasopressor agent could reduce the rate of death among patients in shock.¹³

In the analysis of the effects of groups for inotropes/vasopressor combination, i.e.1. Dopamine + Noradrenaline, 2. Dobutamine + Noradrenaline on CO, SVR, CP, we noticed that there were

Table 1
Baseline characteristics.

Variables	Group 1 N = 38(63.3%)	Group 2 N = 15(25%)	Group 3 N = 6(10%)	p-value
Age	56.05 ± 13.09	57.8 ± 14.9	61 ± 11.66	0.68
Gender				
Male	27(71.1)	12(80)	4(66.7)	0.83
Female	11(28.9)	3(20)	2(33.3)	
Smoking	16(42.1)	4(26.7)	0	0.17
Hypertension	7(18.4)	3(20)	1(16.7)	0.97
DM-II	14(36.8)	3(20)	1(16.7)	0.49
LVEF	27.22 ± 7.51	26.67 ± 4.08	30.83 ± 8.01	0.42

Table 2
Group wise differences in the mean of various parameters at 24 h from baseline between 3 groups (Secondary outcomes).

Details	GroupWise differences in the mean from baseline to 24 h			p-value
	Group 1 N = 38	Group 2 N = 15	Group 3 N = 6	
Cardiac output(L/min)	0.71 ± 0.38	0.60 ± 0.31	0.56 ± 0.51	0.49
SVR(dyne/cm ⁻⁵ /m ²)	90.74 ± 161.19	103.20 ± 188.09	237.17 ± 192.19	0.16
Cardiac index(L/min/m ²)	0.39 ± 0.18	0.33 ± 0.16	0.31 ± 0.29	0.43
MAP(mmHg)	11.66 ± 5.25	11.07 ± 4.5	16.17 ± 7.36	0.12
CVP(cm.)	-3.42 ± 4.79	-3.20 ± 3.8	-2.67 ± 4.08	0.93
Cardiac Power (W)	0.2 ± 0.08	0.17 ± 0.05	0.21 ± 0.14	0.42

*p-value <0.05 shows statistically significance, *SVR, systemic vascular resistance, † MAP, mean arterial pressure, ‡CVP central venous pressure.

Table 3
IABP used in 3 groups.

	Group 1 N = 38(%)	Group 2 N = 15(%)	Group 3 N = 6(%)	p-value
IABP	22(57.9)	6(40.0)	2(50)	0.27

significantly favorable changes in CO and MAP with the titration of dosages of Noradrenaline over time in both the groups, however the mean change in CO, CP, SVR over time did not vary significantly between the two groups. Similarly, a randomized study comparing dopamine with noradrenaline in shock showed that the arrhythmias were more frequent in the dopamine group, and the drug needed to be discontinued more often due to serious arrhythmia, and the outcome was worse in this subgroup with CS.^{14,15}

Noradrenaline is the most commonly used vasopressor; a finding in line with the current recommendations.^{16,17} In the landmark trial SOAP2, it was found on subgroup analysis that in patients with cardiogenic shock, patients with Noradrenalin fared better than dopamine in terms of short term mortality outcomes.¹³ In our study, Noradrenalin was used in titration against background of either Dopamine (group1) or Dobutamine (group2). The group with dobutamine plus noradrenalin titration did significantly better in terms of preventing the in hospital mortality (P 0.004) but it may not be truly reflective of superiority of any regime over other and it may have been confounded by multiple factors especially sicker patients as was reflected in trends differing values of presenting serum Lactate between the various groups.

The groups in our study did not defer significantly in terms of mean change in cardiac output, SVR, and Cardiac Power over time. This result was similar to what was found in Levy et al, which compared MAP in patients with epinephrine vs noradrenaline and dobutamine, where it did not find any significant change.¹⁸

In the study by Francis et al, lesser vasoconstrictive effect was observed with dobutamine as compared to dopamine for a similar rise in cardiac output.¹⁹ In our study Dobutamine was used along with Noradrenalin and hence no significant change in SVR at 6 or 24 h is noted between dobutamine + noradrenaline and dopamine + noradrenalin arms. Also in a study by Richard et al, similar changes in CO was noted in group comprising of Dopamine plus dobutamine vs dopamine alone suggesting us that a similar rise in CO could be achieved with various inotropes and vaso-pressors either alone or when used in combination.²⁰ There was a significant change in terms of mortality outcome in between the 2 groups. The in hospital mortality of the whole cohort of patients with CS in our study was 55%.

The recent literature showing a potential increase in mortality with dopamine over norepinephrine has questioned the use of dopamine as a first line agent in cardiogenic shock.¹⁴ Both dopamine and norepinephrine can cause increased myocardial oxygen demand and may aggravate ischemia. This can lead to arrhythmias making it important to titrate to the lowest dose needed to improve tissue perfusion. For patients who are in a low output cardiogenic shock dobutamine may be added to optimize cardiac output (CO). However, dobutamine can cause vasodilation; therefore, its use should be in patients with less severe hypotension or in combination with a vasopressor to improve cardiac output (CO) in severe hypotension.^{11,13,21}

As noted in IABP shock 2 trial, the use of IABP was not associated with any mortality benefit, which is similar to what we saw in our study.⁷ IABP was used in 50% of our cohort and it did not show any significant difference on in-hospital mortality for the study though this could have been confounded by the study design and smaller sample size. The use of IABP was not associated with significant changes in CO, SVR and CP as compared with the group not

Table 4
Mean doses of inotropes/vasopressors used with or without IABP.

	IABP present N = 30	IABP absent N = 30	p-value
Dopamine(mcg/kg/min)	16.43 ± 16.39	15.4 ± 6.92	0.75
Dobutamine(mcg/kg/min)	4.08 ± 1.41	7.92 ± 2.52	<0.0001*
Nor-Adrenaline(mcg/min)	6.43 ± 2.42	7.55 ± 2.55	0.09

*p-value <0.05 shows statistically significance.

Table 5
Comparing Lactate levels, S. creatinine and mortality amongst the group.

	Group:1 N = 38	Group:2 N = 15	Group:4 N = 6	p value
Lactate(mmol/l)	6.99 ± 4.67	4.07 ± 1.86	6.0 ± 6.06	0.09
S. creatinine(mg/dl)	1.62 ± 0.64	1.72 ± 0.90	1.99 ± 0.79	0.5
Troponin-I(ng/ml)	31.89 ± 32.99	14.68 ± 18.98	28.24 ± 20.72	0.16
Discharge	13(34.2)	12(80)	1(16.7)	0.004*
Expired	25(65.8)	3(20)	5(83.3)	

*p-value <0.05 shows statistically significance.

receiving IABP; however, the dose requirement of dobutamine (49%) was significantly lower in the patients on IABP.

Though the statistically significant difference in mortality was seen between the groups, it may not necessarily suggest that combination of background dobutamine with Noradrenaline titration was better strategy rather than any other regimes as there are confounding factors like sicker patients in group 1. There was no significant difference amongst baseline s. creatinine (1.62 ± 0.64 , 1.72 ± 0.90 and 1.99 ± 0.79 mg/dl; $P = 0.5$) as shown in Table 3 and there was a trend towards lower mean baseline serum lactate levels (6.99 ± 4.67 , 4.07 ± 1.86 and 6.0 ± 6.06 mmol/l; $P = 0.09$).

To our knowledge, this is the first ever study to evaluate various inotropes combinations in CS with NSTEMI especially amongst Asian Indians.

6. Conclusion

The mean changes in hemodynamic parameters were not statistically different between the 3 groups. All the 3 regimes of inotropes when selected as per clinical indication in CS with ACS resulted in similar hemodynamic effects. The mortality difference may not truly be reflective of regimes and may reflect sicker patients in the higher mortality group. Hemodynamic impact of IABP resulted in around 49% lower usage of dobutamine in the cohort.

7. Limitations

This was a single Centre nonrandomized, observational study with small sample size not powered to look for impact on hemodynamics of various regimes. Selection bias due to open label design could have influenced the outcomes of the study especially with regards to usage of Dobutamine or any other inotrope. Various other Confounders and degree of ischemic burden in individual cases may also have contributed to the outcome. The study has a potential confounding if any, that may be inherent to the techniques of measurement of CO and other parameters involved in measurement of hemodynamics and hence it's reproducibility using any other methods may not be in complete correlation with our results.

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Inform consent statement

Written informed consent was obtained from all patients and/or relatives enrolled into the study. No animal studies were carried out by the authors for this article.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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