

## Why is an IABP not the Answer to Cardiogenic Shock after Percutaneous Coronary Intervention? Is it that Noradrenaline helps, Especially by Improving the RV Function in Addition to LV Function? A View Point

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### Abstract

We review the role of noradrenaline in cardiogenic shock. We describe our experience with the same after percutaneous coronary intervention, mostly primary angioplasty.

The side effects of noradrenaline, the results of the SOAP 2 and the IABP Shock trial are also discussed. Noradrenaline is surprisingly a useful drug. So we want to share our experience with it.

**Keywords:** Cardiogenic shock; Noradrenaline; Percutaneous coronary intervention; Primary angioplasty; Inotropes

### Introduction

Randomized trials often reflect the truth but we may not have given them the correct questions. Many post myocardial infarction cardiogenic shock maybe due to a concomitant right ventricular infarction. Even anterior wall myocardial infarction is associated with some amount of right ventricular infarction.

IABP is known to unload the left ventricle and improve the left sided perfusion. Logically after a percutaneous intervention this should improve the survival of a patient. But strangely the Shock two trial negates this hypothesis [1]. It is possible that the missing link is that the survival in the placebo arm was improved by the use of inotropes, maybe the inotrope noradrenaline.

We briefly discuss this theory (postulated by others) [2]. We also describe our experience with noradrenaline in 4 cases who presented to us with a blood pressure less than 65 mm Hg, systolic, for more than half an hour. We also review the findings of the SOAP II trial [3].

### The IABP SHOCK 2 Trial

IABP did not reduce 30 day mortality compared to the placebo [1]. This was a randomized, open label, multicentre trial. This study included both medically treated patients with myocardial infarction as well as those who had primary PCI. Between June 2009 and March 2012, they enrolled 600 patients in the IABP arm (301) and placebo, or control arm (300 patients). In this study 95.8% of patients had primary percutaneous intervention. Interestingly approximately 89.7% of patients in both the IABP arm and the control arm were already on inotropes before randomization. In this trial there was a crossover of randomized patients. 26/299 patients who were assigned to medical management had IABP insertion. But we feel the control arm had the advantage. The mortality reduction may have been caused by the inotropes given. We have not been able to determine the exact doses of the inotropes given to individual patients but the better option might have been noradrenaline. Strangely the IABP arm had more new onset renal failure [4]. In this trial 154/296 patients had 3 vessel disease (52%) in each arm and LAD disease in 45% in the IABP arm and 41.3 % in the control arm. But the right coronary artery disease was seen in 73/293 (24.9%) in the IABP arm and 79/293 in the control arm. It is the inotropes in these patients that might have improved on survival and negated the difference between the two arms. To summarize,

surprisingly better results in the placebo arm may have confounded the results.

Price LC et al. [2] have very nicely described the response of the right ventricle in response to inotropes. They have highlighted the ICU management of RV dysfunction as having the following steps-1) Infusing fluids with caution so as not to increase the RV after load. 2) Using inotropes to improve the RV function, Maintaining AV synchrony, and 3) using oxygen to reduce the pulmonary vascular resistance, 4) maintain the Left ventricular cardiac output and aortic root pressure to adequately perfuse the coronary arteries. IABP maintains only the aortic pressure. It does not augment the right ventricular output as noradrenaline may. These authors have highlighted an interesting point. Increase in the PVR (pulmonary vascular resistance) to a level more than the SVR (systemic vascular resistance) has been found to be detrimental to RV function. This reduces the perfusion to the right coronary artery which becomes only diastolic flow. (Normally the right coronary artery is perfused both by systolic flow or diastolic flow.) Noradrenaline is a predominantly alpha adrenergic receptor agonist so it increases the blood pressure and the systemic vascular resistance and improves the coronary perfusion.

### Our Experience

We have already sent for publication our small series of cardiogenic shock patients who were on noradrenaline (under consideration for publication). We had a mortality of 27% among 11 patients. All patients who had a blood pressure of less than 65 mm Hg, systolic in spite of dopamine and fluids were included and started on 1-4 microgm/mt of noradrenaline to maintain their blood pressures with noradrenaline. Surprisingly we also had 12 patients who had low blood pressures,

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but these resolved only with dopamine. The patients whose blood pressure improved only with dopamine seemed to have only CAD with inferior wall MI and right ventricular myocardial infarction. Strangely a majority of the patients who needed noradrenaline had more anterior wall myocardial infarction.

We would like to describe 4 more patients in whom we used noradrenaline. This is basically to highlight the usefulness of noradrenaline in hypotensive patients, especially after percutaneous intervention. We believe all cardiogenic shock patients should be taken up for percutaneous intervention, but we do not advocate inserting an IABP for all though we do have the facilities, as after the SHOCK 2 trial it is of dubious benefit [1]. All patients with cardiogenic shock who are willing for the procedure are taken up for PCI in our centre (24x7) some of them, including ventricular septal rupture patients have been put on IABP. But the vast majority have been managed with inotropes. (Why? For three reasons, one is the SHOCK 2 trial, two, because of cost constraints [3], some patients have very small femoral arteries).

### Patient 1

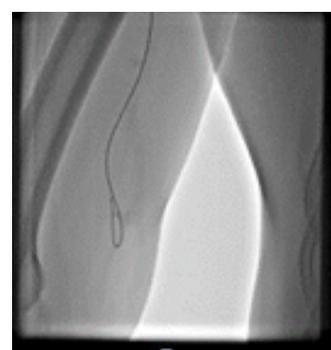
Our patient was Mr D our patient who had CAD acute anterior wall MI and was thrombolysed with intravenous streptokinase in a local hospital. He was transferred with acute left ventricular failure and hypotension so we planned a rescue PCI. His electrocardiogram showed first degree heart block, right axis deviation and right bundle branch block (partial trifascicular block). On CAG his LMCA was normal. This bifurcated into an LAD and a LCX. The mid LAD was totally occluded after an ectatic segment with a thrombus. An attempt was made to cross the LAD with a BMW Universal II wire but on thrombus aspiration with a (Clear hunter 6F catheter). It was found that that vessel was a large diagonal. After that another wire was used to cross into the LAD. The LAD was also aspirated with thrombus aspiration. But in spite of doing this repeatedly the LAD and the diagonal had no reflux (Figures 1-4). So after giving intracoronary tirofiban the procedure was stopped (Figures 5-7). At this time the patient had a blood pressure of 60 mm hg (Systolic). So the patient was started on dopamine, and since the blood pressure did not rise within 30 minutes intravenous noradrenaline was started. His blood pressure rose and then he was started on intravenous furosemide, and two days later spironolactone was started. Two days later he was started on intravenous heparin. With this his bifascicular block disappeared and he was started on half a tablet of 3.125 mg carvedilol. But he still needed noradrenaline as this could not be weaned off. He was on noradrenaline for a total of 10 days but is now stable. He was on 2.5 mg per day of Ramipril and had



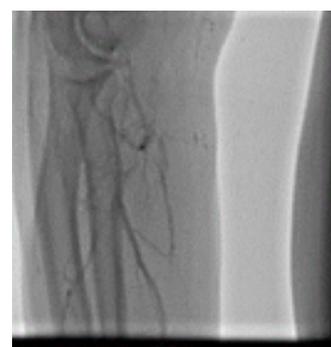
**Figure 1:** The left coronary angiogram of patient 1 showing total obstruction of the mid Left anterior descending coronary artery (The RAO caudal view).



**Figure 2:** Another view of the same patient's left coronary angiogram showing the dilated left anterior descending artery, showing an abrupt cut off due to thrombus.



**Figure 3:** The coronary angiogram showing the guide-wire in the newly opened up diagonal branch.



**Figure 4:** The LAO cranial view showing another guide-wire in the left anterior descending coronary artery, the left circumflex is dominant.

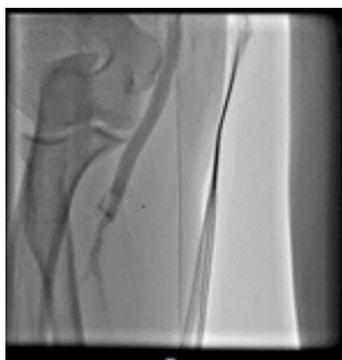
no third heart sound or features of heart failure. His ejection fraction was around 35% (Subsequently, two weeks after discharge, the check angiogram was done, and his LAD was stented).

### Patient 2

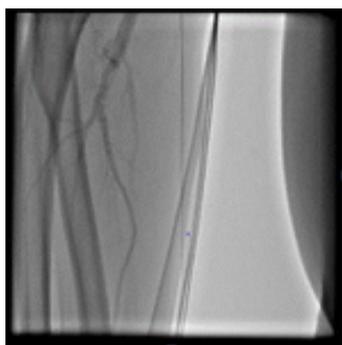
Was Dr. R, who had CAD two vessel diseases, who had discontinued dual antiplatelets after stenting of the right coronary artery and LAD in 2009. He had a right nephrectomy under epidural anaesthesia that was completed one hour before he presented to us with CAD acute inferior wall MI, cardiogenic shock with a blood pressure of 60 mm Hg, systolic in 2014. We did a check angiogram which showed his right coronary



**Figure 5:** The AP cranial view showing no reflux in the left anterior descending coronary artery, At this time the patient's blood pressure was around 54 mm hg systolic.



**Figure 6:** No reflux of both the LAD and the large diagonal. The procedure was abandoned as he had very low blood pressures.



**Figure 7:** Again no reflux. Adenosine, intracoronary or nitroglycerine was not tried as he had low blood pressure.

artery was completely occluded and did a thrombus aspiration and opened up the vessel adequately. We did not look at the other vessel as he seemed stable but his BP was only 60 systolic. So he was started on noradrenaline and he had to be ventilated. He was ventilated for 24 hours and then weaned from the ventilator at 24 hours. But his initial S creatinine was found to be 9 mg/100 ml and in spite of his blood pressure being maintained at 90 mm Hg he expired after 48 hours when he was taken for dialysis (haemodialysis). So noradrenaline increased his blood pressure but could not save the patient. He had a hypernephroma. It is possible the unilateral nephrectomy, the dye and

the hypotension may have injured his remaining kidney. In the last 24 hours of life he had only 200 ml urine and his pH was 7.2.

### Patient 3

Patient 3 was Mr. S. He had had a CAD Old ant wall myocardial infarction, with left ventricular dysfunction and a stenting had been done to his LAD about 4 years back. In April 2014 due to worsening left ventricular function he had a check angiogram that showed a 70% in-stent restenosis and he was resented about 3 months before this incident. He presented with continuous vomiting and gastroenteritis and was transferred to our ICCU with a blood pressure of less than 40 mm systolic. The automated NIBP machine could not register any blood pressure initially. After that he was started on intravenous dopamine and noradrenaline. His blood pressure rose to 90 systolic, he started having urine output and he was ultimately weaned from noradrenaline after 9 days and sent home. He has been stable since then. His ejection fraction has been 29% for the last few years.

### Patient 4

Patient 4 was Mr. AR who had a primary angioplasty for anterior wall myocardial infarction in the Middle East, was ventilated and had bed sores due to being in an overseas ICCU. He presented with a blood pressure of 60 systolic on dopamine from a medical unit. We found that his ejection fraction was 33%. He also survived after being on noradrenaline for 9 days (A 2014 patient). So our mortality was only 25%.

#### Why does noradrenaline work so well?

#### So what makes noradrenaline so perfect for cardiogenic shock?

Noradrenaline does not increase the heart rate as much as dopamine does. It increases the systolic blood pressure and improves coronary perfusion [3] (Tables 1-3).

Noradrenaline does not cause arrhythmias like dopamine. According to the SOAP 2 trial, a significant number of patients had to stop dopamine as they had significant arrhythmias. (More patients on dopamine developed atrial fibrillation). Further noradrenaline caused a mortality benefit [3] (Soap trial). This trial had 858 patients assigned to dopamine and 821 patients to noradrenaline. Overall there were no differences in the 28 day survival of patients with noradrenaline but when the cardiogenic shock arm was taken there were positive results. Overall those on dopamine had more arrhythmic events (207 events, 24.1%) compared to 102 events (12.4%) in the noradrenaline arm,  $p < 0.001$ . In 280 patients with cardiogenic shock also there was more death in the dopamine arm at 28 days. The main arrhythmia was atrial fibrillation. The authors also noted ventricular tachycardia and

N=11
M: 8
F: 3
Mortality: 27%
The mean age of the patients presenting with cardiogenic shock was $59.81 \pm 12.92$ years.
The mean heart rate before dopamine was: $90 \pm 13.77$ /minute
Mean heart rate on dopamine but before noradrenaline-(B) $90 \pm 13.77$
Mean heart rate after dopamine $-87.9 \pm 14.13(a)$
The mean heart rate after noradrenaline was $-83.72 \pm 26.08(C)$

**Table 1:** Unpublished data from the ICCU, MCH Trivandrum of patients over an 8 months period with admission systolic blood pressure less than 60 mm Hg, for more than half an hour on dopamine 20 ml per hour (400 mg in 500 ml 5% dextrose) (These patients were given intravenous noradrenaline).

The mean blood pressure was 74.36 ± 9.79 mm of Hg.
The mean peak dose of dopamine was -11.2 microgram/kg/mt (± 1.2).
Mean Blood pressure after dopamine -74.36 ± 9.7 mm Hg(A)
Mean Blood pressure on dopamine but before starting noradrenaline was -(B) 82.54 ± 7.13.
The mean blood pressure after noradrenaline-98.54 ± 11.50, ©
The mean duration of dopamine infusion was 46.72 ± 28.05 hours and the mean duration of noradrenaline was -23.8 ± 15.85 hours.
The mean dose of noradrenaline: was 4.18 ± 1 microgram/mt
T test A vs. C =p< .0005. B vs. C p<.002.

**Table 2:** Unpublished data in patients with a systolic blood pressure of less than 60 for more than half an hour on 20 ml/min intravenous dopamine (400 mg in 500 ml 5% dextrose) N=11.

Variable	Dead (3)	Alive (8)	
Males	1		
Females	2		X2-NS p<.1
Mean age	57 ± 6.4	60.8 ± 14.48	T test -NS
Duration dopamine	46 ± 32.1	47 ± 26.4 (hours)	
Duration Noradrenaline	21.5 ± 10.4		NS
Mean dose dopamine	10.6 ± 0.94 mcg/kg/mt	11.5 ± 1.3	
Mean dose noradrenaline	4.3mcg/mt ± 0	4.2 ± 1.2 mcg/mt	
Mean BP on Noradrenaline	90 ± 14.14	101.75 ± 8.3	
Change in Hr with Dopamine	11.55 ± 9.7	8.25 ± 4.29	

**Table 3:** Characteristics of patient who lived and died on both dopamine and noradrenaline infusion, unpublished data 3/11 patients died.

ventricular fibrillation. Both of these were more in the dopamine arm. There were 135 patients in the dopamine arm and 125 patients in the noradrenaline arm.

The SOAP two trial patients were very sick. Their ICCU stay ranged from one to 12 days. Their total hospital stay ranged from 2 days to 28 days. 46% of the deaths were from refractory shock. This study was a well-planned, detailed investigation about the role of inotropes in severe shock. So the noradrenaline arm results in cardiogenic shock can be believed.

The use of this drug can increase in the future.

We also were not using much noradrenaline till about 1 and half hours back. That is why we want to share our results. Surprisingly our cardiothoracic surgeons were using it.

**Withdrawal of noradrenaline:** We have observed death in two patients (one included below) in whom noradrenaline was temporarily discontinued while transporting the patient from the cath lab. We did this thinking that extravasation might occur during transportation. The patient below and another patient (not included) both had extreme blood pressure fall and momentarily unrecordable blood pressures. So now in retrospect, noradrenaline treatment should not be interrupted abruptly, and it should be gradually weaned. In the SOAP II trial one of the causes of death listed is “Withdrawal or withholding of therapy” which I assume is noradrenaline or dopamine (46-50% of the deaths were listed as due to this). So we recommend that noradrenaline not be discontinued until the patient is really stable.

**More about noradrenaline:** In a study comparing dobutamine-noradrenaline versus epinephrine in dopamine resistant cardiogenic shock, it was found that epinephrine treated group had higher lactates, more arrhythmias [5]. 6 hours after epinephrine infusion the serum lactate increased but decreased in the noradrenaline group. The splanchnic circulation can be assessed by the tonometered PCO2

gap. This increased in the epinephrine group and decreased in the norepinephrine group. The urine output increased in both groups but significantly more in the norepinephrine group.

This study was conducted in a university medical hospital. It was an open label randomized study. All the patients had an entry blood pressure of 60 mm systolic on dopamine and dobutamine.

New guidelines are available on choosing the inotrope for cardiogenic shock, (Cir) [6].

The dose recommended has been described. They recommend that 4 mg of noradrenaline, or 8 mg of norepinephrine bitartrate (2 mg is equivalent to 1 mg of norepinephrine) to 250 ml of 5% dextrose with or without saline, this results in a concentration of 16 microgm/ml of norepinephrine, or 32 microgram/ml of norepinephrine bitartrate. One should start with low doses and then gradually increase the doses.

Care should be taken to avoid extravasation. Extravasation should be treated with 5 to 10 mg of phentolamine in 10 or 15 ml saline. This should be infiltrated locally.

Overgaard [7] has reviewed inotropes. He also reports that the effect of noradrenaline on the cardiac output is minimal. So probably this is why it can be tolerated by acute myocardial infarction patients. Further it does not increase the heart rate significantly, especially when compared to the effect of dopamine [3]. So it may not significantly increase the oxygen consumption. This may be the secret of its beneficial effect.

#### The side-effects and adverse effects of noradrenaline?

Some authors have commented on the adverse effects of noradrenaline. Jakob has commented that giving noradrenaline for 1 hour in patients with a blood pressure of 65 mm Hg might have been harmful [8]. He postulated that noradrenaline would cause ischemic reperfusion injury, would release the tumour necrosis factor alpha via alpha adrenergic stimulation. The doses he commented on were >2.6 microgm/kg/min (from 1.5 microgm/kg/mt to 2.6 microgm/kg/mt)

Tweet and co-worker have described SAM and LVOTO obstruction after high doses of norepinephrine in a case of CAD acute STEMI following a trauma. So if a cardiogenic shock patient worsens on noradrenaline a timely echocardiogram showing LVOT obstruction and withdrawal of inotropes will help the patient [9].

Tehrani et al. have commented on IABP and cardiogenic shock in a review article. In the Gusto I trial the use of IABP in cardiogenic shock was 35% this increased to 47% in GUSTO III. It was believed that only patients with borderline haemodynamics improved with IABP and the really sick cardiogenic shock patients did not improve [10]. They have commented that in established cardiogenic shock IABP is of dubious value. These authors prefer ECMO or LVADS.

Finally norepinephrine has some advantages when used in high doses [11]. Garg et al. have commented that the brain and its blood vessels have only a few adrenergic receptors, high doses of norepinephrine can safely maintain cerebral perfusion without causing dangerous vasoconstriction and compromising circulatory flow.

We have also observed that obtunded patients with cardiogenic shock often improve and become more conscious on noradrenaline, but we did not know that there is a hemodynamic explanation for this. The patients are seldom agitated or anxious but appear brave, calm and conscious even if they die. Our hearts break to see some of these brave men and women die, they are conscious to the end.

### What is refractory shock? [12]

Bassi et al. have reviewed refractory shock and they have described it as shock requiring more than 0.5 microgram/kg min of noradrenaline or those who required both noradrenaline and vasopressin to maintain their blood pressure. They also describe some series where usage of 15-100 microgram per minute was required to maintain the blood pressures of the patients. In a series those requiring high dose all died. In our patients we have used upto 4 microgram/minute. Critically ill patients with Multiorgan failure require high doses of noradrenaline and die in spite of therapy [12].

Dores et al. tried to study retrospectively whether the survival from cardiogenic shock improved from the period 1998-2001 to May 2008-2011. Over this period there were no differences in death. But the number of patients presenting before 6 hours increased as did the need for dialysis. The percentages of patient receiving PCI also increased. The incidence of cardiogenic shock was 3.7% in the earlier period and 4.8% in the later period. Noradrenaline was given in 47% of the later group but not in the earlier cohort. The use of dopamine and dobutamine significantly declined ( $p < 0.08$  and  $p < 0.001$ ).

### What is the optimum management of cardiogenic shock?

To conclude, basically the main management of cardiogenic shock is invasive management. A patient presenting any time after a myocardial infarction and cardiogenic shock should have per cutaneous intervention. But the difference is, probably instead of IABP insertion, judicious use of inotropes would help survival. Basically if the patient had a blood pressure of 90 systolic and the features of hypoperfusion, the patient can be managed with intravenous dopamine. If the patient had a blood pressure of less than 80 systolic, dopamine with noradrenaline is advocated. If with noradrenaline, the blood pressure does not pick up probably either vasopressin, or Terlipressin or IABP insertion is recommended [7] (We have not used vasopressin or Terlipressin).

The ideal way to monitor the inotrope dose is simple, the blood pressure increases, the extremities become warm and the hourly urine output starts increasing. If the blood urea was elevated initially this gradually comes down, as does the serum creatinine. We do have invasive intraarterial blood pressure recording, but only occasionally need it (It was used in patient number 2). We do not routinely do so,

but the serum lactate levels come down fast if the perfusion to the tissues becomes adequate. As patients improve, they can usually be weaned from the ventilator.

Noradrenaline is an adjuvant to invasive, percutaneous angioplasty for cardiogenic shock due to ACS STEMI.

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