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Clinical Pharmacology of Cardiogenic Shock

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Cardiogenic shock (C.S.) remains an intriguing challenge to the physicians in general and to the cardiologist in particular. Though our understanding of the subject has improved in the last two decades, and availability of newer inotropes and certain mechanical devices have improved the near dismal prognosis, the syndrome remains a formidable challenge in every day practice of a physician working in an acute area. In a well established case where the low cardiac output (C.O) has resulted in prolonged tissue hypoxia death is inevitable. Timely intervention, is thus of paramount importance and is an important factor in determining the ultimate out come. Other factors which affect the prognosis are:

- Extent of myocardial damage.
- Concurrent pathologies like, chronic renal or respiratory disease, fulminating sepsis & other serious diseases.

This article is a review of various inotropes available. I shall restrict myself to a patient where myocardial failure as the cause of shock has been established and all other causes of circulatory collapse have been excluded.

Early recognition of C.S. is important for the treatment to be effective. A patient presenting with evidence of myocardial damage must be closely observed for evidence of dropping C.O. Important clinical clues suggesting impending C.S. are :

- Resting tachycardia
- Restlessness
- Progressive drop in arterial P02 in the absence of any significant respiratory pathology.
- Unexplained diaphoresis.
- Cold extremities.
- Progressive drop in urinary out put provided it is measured hourly.
- Dropping systolic blood pressure (B.P.).

Total reliance on B.P. recorded by cuff method may be misleading and must be ignored if other clinical signs of falling C.O. are present. Thus a very close clinical surveillance is vital to achieve the desirable results.

Objective Of Inotropic Therapy

- Normalize C.O.
- Relieve pulmonary congestion.
- Reduce L.V. dimension
- Improve B.P. & tissue perfusion.
- Improve exercise tolerance.

Achievement of these objectives on one end will improve C.O. and tissue perfusion and on the other end will reduce left ventricular end diastolic pressure (L.V.E.D.P). This will help to improve the diastolic gradient between the aorta and the L.V. and thus will increase the coronary blood flow and myocardial perfusion which is so vital in a failing heart and more so if associated with obstructive coronary artery disease (C.A.D).

Various inotropes available today in Pakistan are:

1. Digitalis Glycosides
   - Digoxin (Lanoxin)
   - Deslanoside (Cedillanid)

2. Catcholamines
   - Dopamine (Intropin)
   - Dobutamine (Dubutrex)
   - Isoproterenol (Saventrine)
   - Norepinephrine

3. Phosphodiesterase Inhibitor
   - Amrinone

In the subsequent pages I shall try to elaborate on the clinical pharmacology of these drugs, highlighting their mechanism of action on various hemodynamic parameters as well as their response when used in combination or with other agents commonly used in patients with failing hearts.

Digitalis

It acts primarily by inhibiting Na - K ATPase pump. This increases available Na for exchange with

extracellular Ca which inturn will increase the force of muscular contractility.

It is given as a loading dose of 0.75 to 1.25 mg over eight to 24 hours. Unfortunately the mechanism of action is not until 30 minutes to two hours after administration. with a peak effect at two to six hours. Thus it is not very useful in acute setting except in the setting of atrial fibrillation with rapid ventricular response, when it will help slow down the ventricular response. It has a prolong half life i.e, 36-48 hours and is excreted primarily by kidney except digitoxin which is metabolized by liver. This limits its use in patients with renal impairment.

It increases C.O. by 5-15% with no significant effect on the systemic vascular resistance (S.V.R) or pulmonary capillary wedge pressure (P.C.W.P). It is thus a relatively weak inotropic in patients with sinus rhythm and is not of much benefit in emergency setting. Side effects are:

- G.I.upset
- Arrhythmias
- Heart Blocks
- Neurological

Its interaction with other commonly used drugs is given in Table-1. Two preparations of this glycoside are available in Pakistan. These are digoxin and deslanoside. Their pharmakinetics, major effects on the electrophysiological properties of heart and factors influencing individual sensitivity to digitalis are given in tables 2, 3 & 4.

Amrinone

It acts by inhibiting phosphodiestrease activity. This will indirectly increase cyclic AMP levels, and hence activate protein kinases thus improving the ventricular contraction.

The drug is given as slow I.V. bolus over 30-45 minutes at 0.75 mcg/kg this is followed by a maintenance dose of 5-10 mcg/kg/min. The onset of action is quick i.e. 2-5 minutes with a peak effect within 10-15 minutes. The half life is 3.6 to 5.8 hours and drug is excreted by the kidneys.

It acts by improving the C.O. which is associated with a reduction in P.C.W.P. & S.V.R. B.P. and heart rate (H.R.) are usually not affected. Caution should be used in patients with a normal P.C.W.P. since its vasodilatory effect may produce hypotension. It is indicated in patients with myocardial failure where prime objective is to reduce preload & afterload i.e., P.C.W.P. & S.V.R. Side effects include thrombocytopenia (2%), arrhythmia (3%), & nausea (2%).

Inotropic Catecholamines

These include:
- Epinephrine
- Nor epinephrine
- Isoproterenol
- Dopamine
- Dobutamine

These drugs stimulate adenylate cyclase which in turn increases production of cyclic A.M.P. This activates a protein kinase which increases Ca transport across the membrane to enhance the myocardial contractility. Increased cyclic A.M.P. also enhances re-uptake of Ca of the sarcoplasmic recticulum. This helps improve the diastolic compliance of the myocardium as well.

Their effects can be divided into two groups.

A) CARDIAC EFFECTS:

This is brought about by $\beta 1$ receptor stimulation and consist of;

- Increased C.O.
- Increased H.R.
- Arrhythmogenic effect

Susceptibility to arrhythmia varies with various compounds & is less frequently seen with dobutamine. All catecholamines listed above have this effect.

B) VASCULAR EFFECT:

This effect is brought about by stimulation of alpha and $\beta 2$ receptors. The former will produce:

- Higher P.V.R.
- Higher B.P.
- Lower C.O.

Norephinephrine, dopamine and epinephrine come in this category. $\beta 2$ stimulation produces a vasodilatory effect resulting in

- Lower P.V.R.
- Lower B.P.
- Hypotension (If the patient is volume depleted).

Isoproterenol is included in this group.

I shall now like to discuss in somewhat greater detail the clinical pharmacology of the two most commonly used cetacholamines.

Dopamine

This drug is given in a diluted solution @ 1-15 mcg/kg/min. The effect varies with the dose & is shown in Table-5.

Table-5.

Dose Mcg/kg/min	Agonist	Effect
1-4	Dopaminergic vasodilatation.	Selective renal
4-8	$\beta 1$	Increases inotropism increases HR arrhythmias
>8	$\alpha 1$	Increases arterial resistance

This drug is most useful in small doses where improvement of renal perfusion is the primary objective. In higher doses it may even deteriorate the hemodynamic status by increasing P.C.W.P., S.V.R., H.R. and lowering C.O. These changes will increase myocardial oxygen demand, which can further deteriorate LV function particularly in patients with active myocardial ischemia.

Dobutamine

This catecholamine is a recemic mixture of equal parts of two isomers i.e., levo & dextro. The levo form is an alpha-I stimulant producing vasoconstriction, whereas the dextro form stimulates $\beta 1$ & $\beta 2$ receptors thus producing increased myocardial contractility & mild to moderate vasodilatation. The sum effect of the two isomers when combined in equal parts is then improved inotropicity with very little change in S.V.R.

This drug is also given in a diluted form as a slow I.V. infusion at 2.5 to 20 mcg/kg/min. Common clinical effects are:

- Improved C.O.
- Lower P.C.W.P.
- Lower S.V.R.
- HR & B.P. (May not change significantly).

Side effects are negligible and include sinus tachycardia and various forms of atrial and ventricular arrhythmias.

Comparison With Dopamine

Leier et al compared the pharmacological effects of the two catecholamines in various hemodynamic parameters. Some of these effects are shown in figures 1.

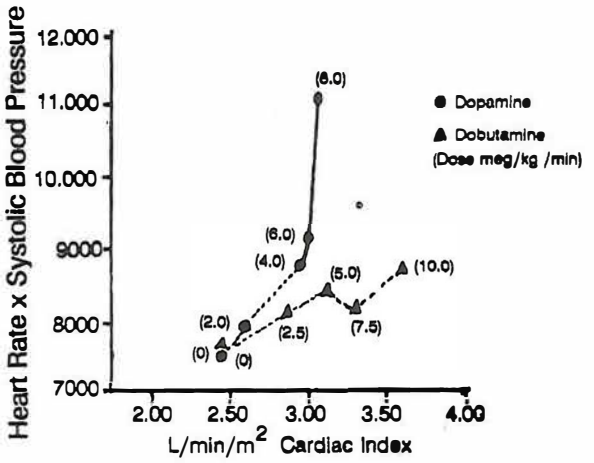

Fig. 1: Comparison of Dopamine and Dobutamine on Heart Rate x Systolic Blood Pressure.

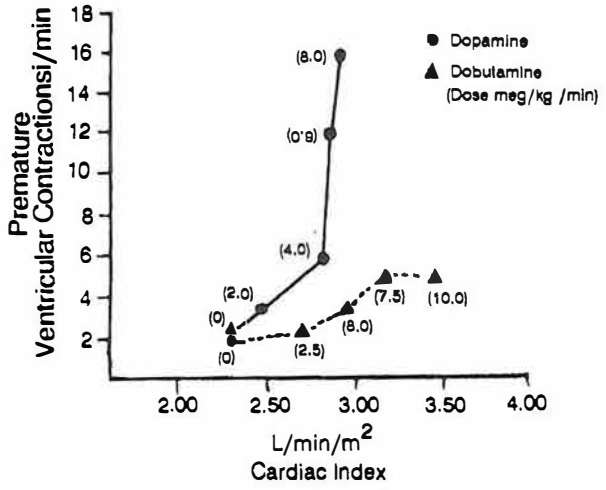

Fig. Comparison of Dopamine and Dobutamine on PVC's

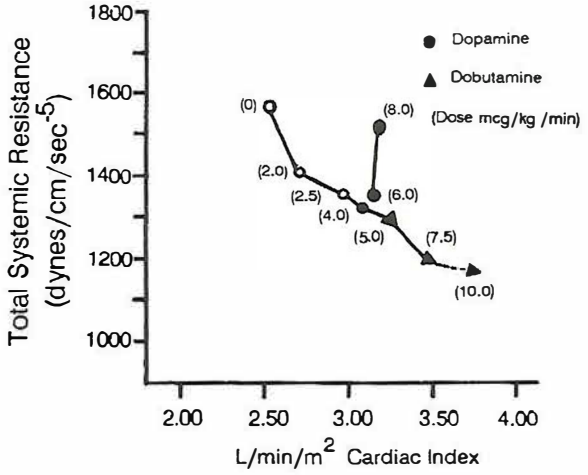

Fig. 3: Comparison of Dopamine and Dobutamine on Systemic Vascular Resistance.

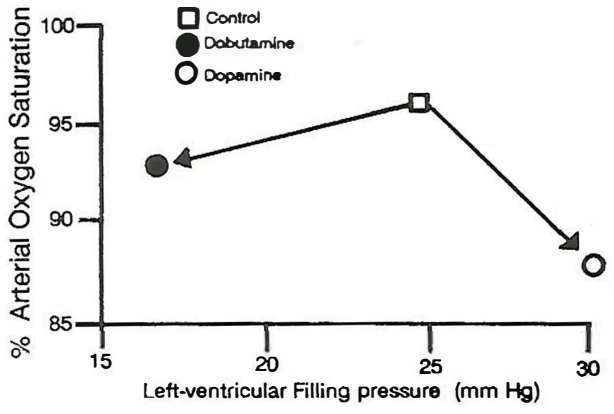

Fig. 5: Arterial Oxygen Saturation as a Function of Left Ventricular Filling Pressure.

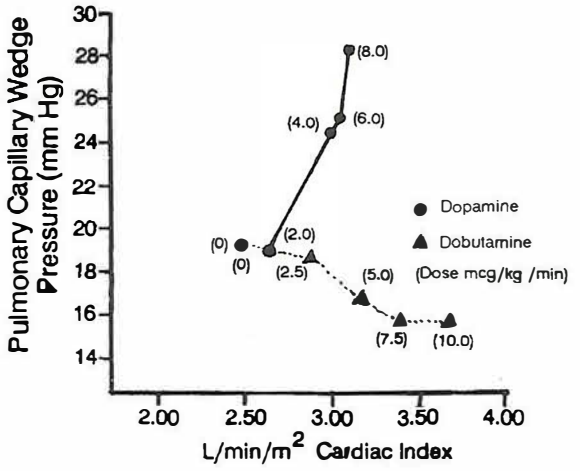

Fig. 4: Comparison of Dopamine and Dobutamine on LV Filling Pressure.

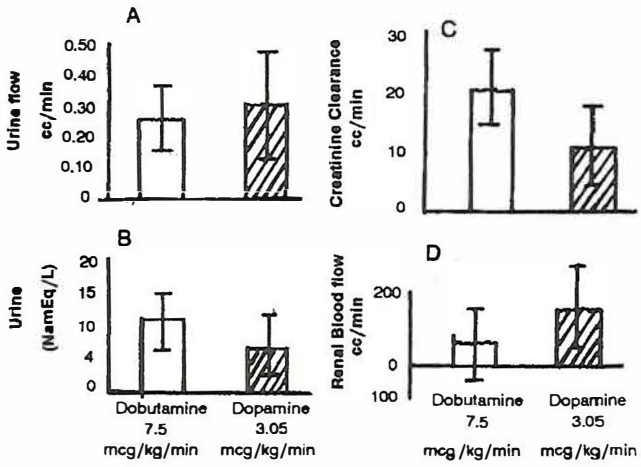

Fig. 6: Effect of Dopamine VS Dobutamine in Renal Failure in the gorup of patients with heart failure.

to 4. It was seen that HR, HR × B.P. product, number of premature ventricular contractions (P.V.C.), S.V.R., P.V.R. & L.V.E.D.P., all increased beyond a certain dosage with dopamine with no significant improvement in C.O. Whereas, with dobutamine these parameters either did not increase significantly i.e. HR, HR × Bp & PVC's or there was a substantial drop in some of these parameters i.e., S.V.R., P.V.R., L.V.E.D.P. Similarly, arterial O_2 saturation as a measure of LV function is not altered after dobutamine infusion but it drops significantly after dopamine. Fig-5.

The effect of dobutamine on renal function in patients with long standing congestive heart failure (C.H.F) demonstrates a significant improvement in urinary flow, creatinine clearance & urinary Na excretion but with no change in renal blood flow. Such improvement is probably the result of increase in C.O. Dopamine alone was unable to show statistically significant change in these parameters. Fig-6.

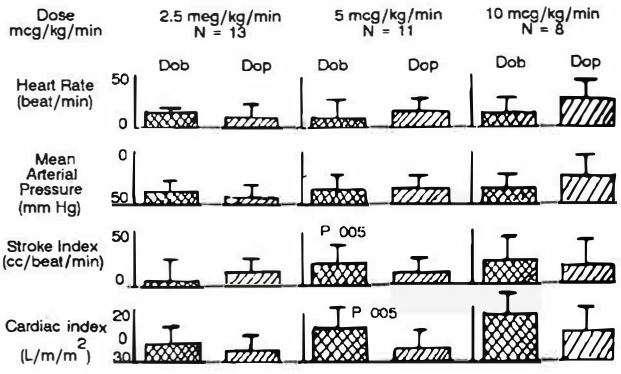

Fig. 7: Hemodynamic Effects of Dopamine vs. Dobutamine in Cardiogenic Shock.

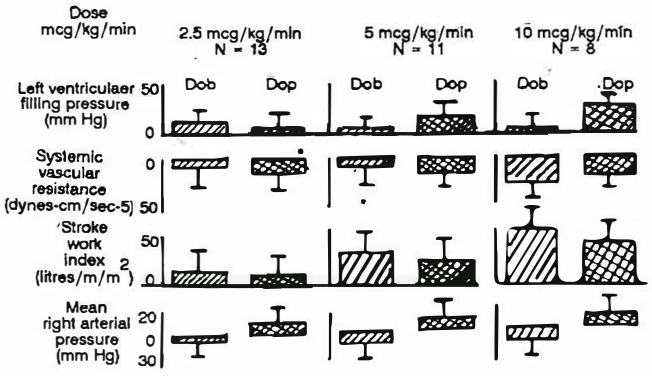

Fig. 8: Hemodynamic Effects of Dopamine vs. Dobutamine in Cardiogenic Shock (Continued).

In patients with cardiogenic shock, Frances et al compared the two drugs. One of the drug was given at 2.5, 5 & 10 mcg/kg/min., for 10 minutes followed by 30 minutes wash out and then administration of the second drug. The results are illustrated in Fig-7-8. It is evident that in small dose (2.5 mcg/kg/min) both drugs are comparable. However, at higher doses dobutamine had a clear margin over dopamine. It improved storke index (S.I.) & cardiac index (C.I.) without any significant rise in the L.V.F.P. Similarly following, cardiac surgery both drugs improved S.I., but with continuous use dopamine produced a significant rise in P.C.W.P., without any improvement in S.I. fig-9.

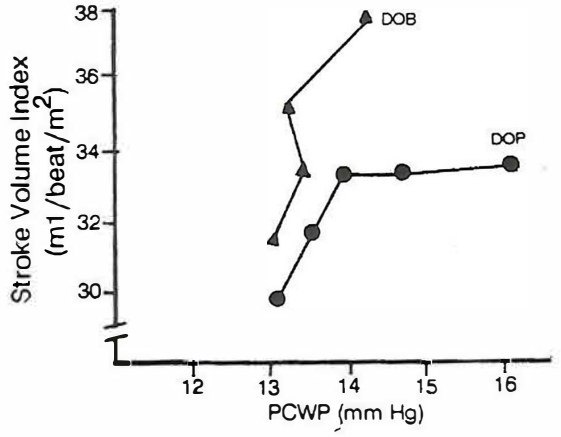

Fig. 9: Comparison of Dopamine and Dobutamine after Cardiac Surgery.

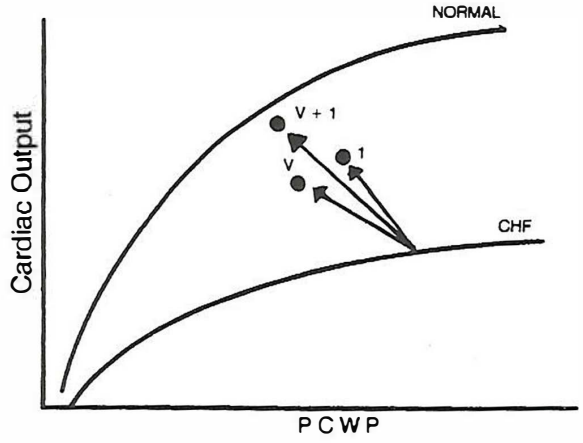

Fig. 10: Effects of Inotropes and vasodilators

Dobutamine & Nitroprusside

The effect is identical on various hemodynamic paramcters i.e., both increase the C.O. at the same time lowering PCWP, SVR and PVR. Lowering of SVR with dobutamine is brought about indirectly by improving the C.O. whereas nitroprusside produces direct effect on the vascular tone. When used together the effect is synergistic i.e., pulling the Frank Starling curve into the left upper quadrant. Fig-10.

Dobutamine vs Amrinone

No appreciable difference was found between amrinone & dobutamine and both drugs produced identical effect on various hemodynamic parameters.

Table-1: Pharmacokinetic Drug Interactions with Digoxin

Drug	Mechanism of Interaction	Mean Magnitude of	Type of Study Single-Dose	Steady	Suggested Intervention
Cholestyramine	Absorption of digoxin	↓ 25%		X	1) Give digoxin 8 hours before cholestyramine 2) Use solution or capsule form of digoxin
Antacids	Unclear	↓ 25%	X		Temporal separation of time of administration
Kaolin-pectate	Adsorption of digoxin	?	X		1) Give digoxin 2 hours before kaolin-pectate 2) ? Use solution or capsule form of digoxin
Bran	Adsorption of digoxin	↓ 20%	X		Temporal separation of time of administration
Neomycin	Unknown	↓ 28%	X		Increase dose of digoxin
Sulfasalazine		↓ 18%	X		
PAS		↓ 22%	X		
Erythromycin Tetracycline (in < 10% of subjects)	↑ Bioavailability by ↓ intestinal metabolism of digoxin by certain gut flora	↓ 43 to 116%		X	1) Measure serum Digoxin concentration 2) Decrease digoxin dose 3) Use solution or capsule form of digoxin
Quinidine	? ↓ Bioavailability, ↓ volume of distribution, ↓ renal and nonrenal clearance	↑ 100%	X	X	1) Decrease dose by 50% 2) Measure serum digoxin concentration
Amiodarone	↓ Renal and nonrenal clearance	↑ 70 to 100%		X	Same as for quinidine
Verapamil	↓ Renal and nonrenal clearance	↑ 70 to 100%		X	Same as for quinidine
Diltiazem	? ↓ Renal clearance	Zero to ↑ 22%		X	None
Nicardipine	Unknown	↑ 15%		X	None
Tiapamil	Unknown	↑ 60%		X	Same as for quinidine
Spironolactone	↓ Renal and nonrenal clearance	↑ 30%	X		Measure serum digoxin concentration
Triamterene	↓ Nonrenal clearance	↑ 20%	X		Measure serum digoxin concentration
Indomethacin (Preterm)	? ↓ Renal clearrance	↑ 50%		X	Decrease dose by 25%

Table-2 Cardiac Glycoside Preparations

Agent	Gastrointestinal Absorption	Onset of Action (MIN)	Peak Effect (HR)	Average Half-Life**	Principal Metabolic Route (Excretory Pathway)	Average Digitalizing Dose		Usual Daily Oral Maintenance Dose
						Oral	Intravenous	
Ouabain	Unreliable	5 to 10	½ to 2	21 hours	Renal; some gastrointestinal excretion	—	0.03 to 0.50 mg	—
Deslanoside	Unreliable	10 to 30	1 to 2	33 hours	Renal	—	0.80 mg	—
Digoxin	55 to 75% 90 to 100%#	15 to 30	1½ to 5	36 to 48 hours	Renal; some gastrointestinal excretion	1.25 to 1.50 mg#	0.75 to 1.00 mg#	0.25 to 0.50 mg
Digitoxin	90 to 100%	25 to 120	4 to 12	4 to 6 days	Hepatic; renal excretion of metabolites	0.70 to 1.20 mg	1.00 mg	0.10 mg
Digitalis leaf	About 40%	—	—	4 to 6 days	Similar to digitoxin	0.08 to 1.20 g	—	0.10 g

Table-3 Some Major Effects of Digitalis on the Electrophysiological Properties of the Heart

Property	Effect
Pacemaker Automaticity	
SA node	→ ↓ (↑ after atropine or toxic doses)
Purkinje fibers	↑
Excitability	
Atrium	→ *
Ventricle	Variable*
Purkinje fibers	↑ *
Membrane Responsiveness	
Atrium	Variable* (↓ after atropine)
Ventricle	↓ (toxic doses)
Purkinje fibers	↓ (toxic doses)
Conduction Velocity	
Atrium ventricle	↑ (slight)*
AV node	↓
Purkinje fibers	↓
Effective Refractory Period	
Atrium	↓ (↑ after atropine)
Ventricle	↓
AV node	↑
Purkinje fibers	↑ *

Table-4 Factors Influencing Individual Sensitivity to Digitalis

- Type and severity of underlying cardiac disease
- Serum electrolyte derangements
  - Hypokalemia or hyperkalemia
  - Hypomagnesemia
  - Hypercalcemia
  - Hyponatremia
- Acid-base imbalance
- Concomitant drug administration
  - Anesthetics
  - Catecholamines and sympathomimetics
  - Antiarrhythmic agents
- Thyroid status
- Renal function
- Autonomic nervous system tone
- Respiratory disease

Dobutamine Vs Digoxin In Acute Myocardial Infarction:

In a study published in 1980 effect of dobutamine given at 9 mcg/kg/min., was compared with full loading dose of digoxin in patient with acute myocardial infarction. Cardiac index improved by 33% with dobutamine vs 9% with digoxin. Similarly PCWP and SVR both fell significantly after dobutamine only.

In patient with acute M.I., dobutamine produced no significant change in the infarct size or number of PVCs.

In summary, I have given a birds eye view of the clinical pharmacology of shock. I have tried to emphasize the effect of these drugs on various hemodynamic parameters hoping that clinical application of this basic knowledge will give better understanding to my younger colleagues and will help them in the management of this potentially lethal syndrome.