New Drugs for Heart Failure

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I. Effect of Heart Failure on Preload and Afterload

Adaptation or compensatory mechanisms generally conceal the clinical signs at the beginning of heart failure (Starling's law). When these mechanisms are exceeded, heart failure may be objectivated: there is an increase in the left ventricular diastolic pressure, and if failure is severe, cardiac output decreases. These haemodynamic changes affect preload and afterload and are responsible for the clinical signs of heart failure.

A. Effect on preload

The elevated left ventricular diastolic pressure is transmitted to the lungs via the left auricle and the pulmonary veins; lung congestion is responsible for dyspnoea (more severe as heart condition deteriorates); right heart failure may then follow left heart failure.

B. Effect on afterload

As an adaptative mechanism to a decrease in cardiac output there is an increase in the sympathetic tone (sympathetic drugs have a positive inotropic action on the myocardium) with tachycardia and peripheral vasoconstriction, which increases the afterload; this mechanism helps to maintain the blood pressure but at the price of a high energical cost (myocardial oxygen consumption increases). When this mechanism fails, the cardiac output decreases with secondary effects: fatigue, postural hypotension, decreased diuresis (with salt and water retention), etc...

II. Treatment of Heart Failure

The classical treatment includes diuretics, digitalis, low salt diet, rest. We intend to review briefly some of the new approaches of heart failure treatment. These new drugs may increase myocardial contractility; others have a venous or an arteriolar vasodilating effect; some have several sites of action.

1. Drugs Increasing Myocardial Contractility

A. Sympathicomimetic drugs

DOPAMINE

At low doses (2-3μg/kg. min), dopamine shows a positive inotropic action, with an increase in diuresis (increased renal flow), and only a little or no arteriolar vasoconstriction. With high doses, the diuresis is not always increased, and an arteriolar vasoconstriction is observed, inducing high peripheral resistances (afterload) and increasing myocardial oxygen demand!

Administration: continuous infusion(2-3 μg/kg min). Haemodynamic monitoring is preferable, but not mandatory.

Adverse reactions: tachycardia, arrhythmias, angina, arteritis, nausea.

Indications: shock, refractory heart failure with fluid retention.

DOBUTAMINE

In comparison with dopamine, this synthetic beta-adrenergic agent does not increase the heart rate to the same extent but has the same effect on cardiac output. The renal effect is much less evident. Dobutamine induces arteriolar vasodilation, thus decreasing the afterload.

Administration: continuous infusion (2.5 to 7.5 μg /kg. min) Haemodynamic monitoring is preferable but not mandatory.

Adverse reactions: tachycardia, angina, nausea.

Indications: refractory heart failure, when afterload is a *"plus point"*; in some cases of myocardial infarction with severe heart failure (refractory to vasodilators or to usual drugs).

SALBUTAMOL - PIRBUTEROL

These drugs may be given orally but it is too early to state yet what will be the place of these drugs in the treatment of heart failure.

B. **Other drugs**

AMRINONE

Amrinone increases the cardiac output, reduces the pulmonary wedge pressure, with variable evolution of the heart rate and the blood pressure. It may be given orally and intravenously. Cases of thrombocytopenia are reported after amrinone.

SULMAZOL (AR-L 115)

This new drug, not yet commercially available, is of great interest. The positive inotropic action is potent; in most of the cases heart rate is not increased and arteriolar vasodilation is observed, a good answer to most of the prerequisites of the *"ideal drug"*. Furthermore, it may be given orally or intravenously. More experience is needed to evaluate the side effects.

2. **Vasodilating Drugs**

A. **Venous vasolidating drugs**

The purpose is to lower the venous return to the heart, decreasing the pulmonary wedge pressure (preload). Such an effect is obtained with diuretics (reduction of blood volume), tourniquets, bleeding. The venous dilating drugs are pooling blood at the periphery.

FRUSEMIDE

Apart from the well-known diuretic action, frusemide induces venous dilation, and a very effective pooling when given intravenously.

INTRAVENOUS NITRATES

Given intravenously (nitroprusside, trinitrine) they are very powerful, nitroprusside showing also an effect on the arteriolar side. They induce generally some degree of tachycardia. Due to their very potent action, haemodynamic monitoring is mandatory.

ORAL NITRATES (trinitrine, isosorbide dinitrate)

They induce venous pooling with some arteriolar reaction; acceleration of the rhythm may be observed. Due to the short duration of action (about 4h for isosorbide dinitrate), 20, 40 or 60 mg are to be given 6 times a day. Nitrates may also be given by cutaneous ointment.

B. **Arteriolar vasodilating drugs**

The aim of these drugs is to reduce peripheral resistance, facilitating the left ventricular emptying, increasing the systolic output (and cardiac output). If the heart rate remains stable, this result is obtained without an increase in the myocardial oxygen demand. The use of these drugs should be avoided in severe hypotension, and the blood pressure has to be checked.

PHENTOLAMINE

The alpha-blocking effect of phentolamine is responsible for a clear arteriolar vasodilation with some venous action too. The effect is comparable to nitroprusside but the impact on afterload is more potent (increase in cardiac output), with less effect on pulmonary wedge pressure.

Phentolamine has to be given by continuous venous infusion (10-40 mg/h). Monitoring of Haemodynamics is preferable, however, heart rate and careful peripheral blood pressure observations are usually sufficient.

HYDRALLAZINE

Hydrallazine acts directly and almost only on the arteries. This oral drug has to be given at increasing doses (25 to 50 mg, 3 to 4 times a day); the limiting signs are tachycardia and a fall in blood pressure (some decrease may be very useful). Lupus and polyneuritis were reported after long term treatment with high doses.

PRAZOSIN

The alpha-blocking effect of prazosin results in a balanced arterial and venous vasodilation, affecting preload and afterload. Given orally, the first doses are to be given in the evening (0.5 mg) to avoid hypotension. The dose is progressively increased till 2 to 5 mg. four times a day.

Headache, vertigo, orthostatism, tachyphylaxia are reported.

CAPTOPRIL

This new hypotensive drug (inhibiting the renin-angiotensin system) seems to be very promising in heart failure; low doses are to be given (12.5 or 25 mg, 3 times a day). Cutaneous rash has been reported.

III. **Conclusions and Summary**

Drugs increasing myocardial contractility have a drawback: the increased myocardial oxygen demand. This may be a problem in ischaemic heart disease. Nevertheless, research in this area shows a clear improvement: dobutamine has also a vasodilating action, Sulmazol avoids the increase in the rate and is also an interiolar vasodilating drug! These drugs may be very useful in severe cardiac disease, particularly when hypotension prevents the use of vasodilating drugs.

Venous vasodilating drugs will affect mostly the preload, with a reduction in the pulmonary wedge pressure relieving dyspnoea. Given intravenously, this very powerful activity necessitates haemodynamic monitoring; fortunately, the oral drugs are effective, but high doses are needed and due to short action, they are to be given approximaely four hourly.

Arteriolar vasodilating drugs reduce peripheral resistances (afterload), increasing the cardiac output without increase in the myocadrial oxygen demand.

Some of these new drugs have several sites of action: venous and arteriolar vasodilation (Prazosin), myocardial contractility and arteriolar vasodilation (Dobutamine, Sulmazol). They may also be given simultaneously, to act on preload, contractility and afterload.

Nevertheless, diuretics, digitalis, low salt diet and rest remain the basis and the first steps in the treatment of heart failure. The other oral drugs are given if necessary to reach a better result (sometimes digitalis is poorly tolerated or should even be avoided as in actue myocardial infarction). The use of all intravenous drugs is to be restricted to patients refractory to the usual approach.