Myocardial and vascular actions of milrinone

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Milrinone exerts potent positive inotropic and direct vasodilator properties in vitro. Several studies have been undertaken to elucidate the relative contributions of each of these actions to the overall haemodynamic effect of milrinone in patients with congestive heart failure. Intracoronary infusion of milrinone to patients with congestive heart failure results in a dose-related increase in left ventricular filling pressure, \( +dP/dt \), indicating a positive inotropic effect due to direct myocardial stimulation. Infusion of milrinone into the brachial artery increases forearm blood flow and decreases forearm vascular resistance, indicating a direct vasodilator action in patients with congestive heart failure.

The relative contribution of milrinone's positive inotropic and vasodilator actions has been assessed by two approaches. First, the haemodynamic effects of nitroprusside and milrinone were compared at doses that caused equal reductions in arterial pressure. Under this condition, the improvement in left ventricular pump function caused by milrinone exceeded that caused by nitroprusside, suggesting that a significant portion of milrinone's overall effect could not be attributed merely to vasodilatation. Second, the haemodynamic effects of intracoronary and intravenous milrinone administration were compared in the same subjects. Under these conditions, the haemodynamic effect of intracoronary drug infusion accounted for a substantial portion of the improvement in left ventricular pump function. The conclusion from these studies, taken together, is that the overall haemodynamic effect of milrinone is due to significant contributions from both its positive inotropic and its vasodilator actions. Consequently, milrinone differs significantly from pure vasodilators, such as nitroprusside, and relatively pure positive inotropic agents, such as dobutamine.

Basic mechanism of action

Milrinone, an analogue of amrinone, is a bipyridine derivative which selectively inhibits peak-III phosphodiesterase, the predominant form of this enzyme present in myocardium and vascular smooth muscle\(^1\)-\(^3\). Although other mechanisms of action may be elicited at high concentrations in vitro, it appears that the predominant mechanism of action of milrinone in patients is the inhibition of phosphodiesterase, resulting in an increased accumulation of cAMP. In myocardial cells, an increased cAMP level augments the inward conductance of calcium ions via voltage-dependent channels, thus allowing more calcium to enter the cell with each depolarization and resulting in an increased level of contractile force development. In addition, cAMP acts to accelerate the reuptake of cytosolic calcium during diastole, thus increasing the rate and/or extent of myocardial cell relaxation. In vascular smooth muscle, the mechanism by which cAMP causes vasodilatation is not known with certainty, but may involve phosphorylation of myosin light chain kinase and/or an alteration in cellular calcium handling.

Positive inotropic action

Several laboratories have demonstrated a positive inotropic effect of milrinone in man. Baim et al.\(^4\) demonstrated that the short-term bolus administration of milrinone (median dose, 75 \( \mu \)g kg\(^{-1} \)) caused a 28% increase in left ventricular peak \( +dP/dt \) in 10 patients with moderate to severe congestive heart failure. Jaski et al.\(^5\) similarly found that the incremental bolus administration of milrinone in doses of 12.5, 25 and 50 \( \mu \)g kg\(^{-1} \) resulted in a concentration-related increase in left ventricular peak \( +dP/dt \) and stroke volume index in 11 patients with New York Heart Association (NYHA) functional class III-IV congestive heart failure (Fig. 1).
normal subjects without evidence of left ventricular dysfunction, Borow et al. [6] used load-independent end-systolic indices of contractility to demonstrate that intravenous bolus doses of milrinone (30, 45 and 60 \( \mu \)g kg\(^{-1} \)) caused a dose-related increase in several indices of contractility. In addition, it was demonstrated that milrinone produced progressive decreases in total systemic resistance and left ventricular end-systolic wall stress, actions which are indicative of a vasodilator effect.

An increase in +dP/dt has also been observed following oral administration of milrinone. In 12 patients with moderate congestive heart failure, Timmis et al. [7] showed that a 5 mg oral dose of milrinone significantly increased left ventricular maximum +dP/dt (+11%) and dP/dt/P (+68%), the latter being an isovolumic index which is relatively less affected by concomitant changes in loading conditions.

These investigators also demonstrated that the left ventricular end-systolic pressure/dimension relationship was significantly increased by oral administration of milrinone, further supporting a positive inotropic effect of the drug. Piscione et al. [8] likewise found that an oral dose of milrinone caused a significant (15%) increase in +dP/dt, a 33% increase in \( V_{\text{max}} \), and a 50% increase in \( V_{\text{ce}} \) (velocity of contractile elements).

It should be noted that observations regarding +dP/dt may be affected by changes in heart rate, arterial pressure and left ventricular cavity dimensions. Decreases in any of these parameters may result in a decrease in +dP/dt, and, conversely, increases may result in an increase in +dP/dt. Because milrinone is a potent vasodilator which decreases both the arterial pressure and the left ventricular preload, a direct positive inotropic effect of the agent might be expected to be partially or totally obscured by the counterbalancing effects of vasodilatation. This counterbalancing effect would be most pronounced in patients with a markedly reduced filling pressure who are, therefore, on the relatively steep portion of the left ventricular function curve.

Observations on the dose–response relationship of the +dP/dt response to milrinone support this point of view [9]. In 14 patients with moderate to severe congestive heart failure, incremental bolus doses of milrinone (12.5, 25 and 50 \( \mu \)g kg\(^{-1} \)) resulted in an
incremental increase in +dP/dt for the entire group. However, in three of the patients +dP/dt increased only with the first two doses, and then fell substantially with the next higher dose. In these three patients, the highest dose of milrinone resulted in a marked decrease in left ventricular end-diastolic pressure from 25 to 6 mmHg. In the other 11 patients who continued to show an increase in +dP/dt, the decrease in left ventricular end-diastolic pressure was much smaller, from a mean of about 27 mmHg to a mean of 17 mmHg. Because it is highly likely that the higher dose of milrinone would exert a similar or greater positive inotropic effect than the lower doses, the most likely explanation is that in the three patients who showed a marked decrease in left-ventricular end-diastolic pressure, the reduction in preload obscured the direct positive inotropic effect of the drug.

Although a positive inotropic effect of milrinone is well supported by several studies, the relative contribution of the drug's positive inotropic versus vasodilator effects to its overall net haemodynamic action remains unclear. As an approach to this issue, we have utilized the direct intracoronary infusion of the drug to patients with congestive heart failure. Because coronary artery blood flow is only approximately 4–6% of total cardiac output, it is possible to infuse very small quantities of drug into the coronary artery and yet achieve therapeutic drug levels in the myocardium. As a result of the small intracoronary dose, there is little systemic accumulation of drug, particularly if infusion periods are kept brief.

For this technique, a 7-Fr L-4 Judkins catheter is placed in the left main coronary ostium as if for coronary angiography. The catheter is perfused continuously with heparinized saline solution to prevent clot formation. A micromanometer-tipped catheter is placed in the left ventricle to measure pressure and to allow determination of +dP/dt. Cardiac output is determined by the Fick method. The haemodynamic effects of a drug infused by this method can be ascribed to the agent's direct myocardial effects, plus any indirect systemic action due to a change in myocardial function. The major advantage of this approach is that the effects of the agent on arterial pressure and left ventricular filling pressures are minimized or eliminated, and, therefore, left ventricular +dP/dt can be used as a convenient measure of changes in the left ventricular contractile state.

Intracoronary infusion of milrinone results in a dose-related increase in +dP/dt. This effect is associated with a substantial improvement in left-ventricular pump function, as reflected by increases in stroke volume and stroke work, and by small decreases in right and left heart filling pressures (Fig. 2). At an infusion rate of 50 µg min⁻¹ which results in a predicted coronary artery drug concentration that is in the therapeutic range, +dP/dt is increased by 21%, the stroke volume index is increased by 18%, and the stroke work index is increased by 21%. Interestingly, this effect is associated with a significant (−17%) decrease in the left ventricular end-diastolic pressure (Fig. 2). This effect may be due to an improvement in the forward pump function, but is also consistent with the possibility of a direct lusitropic action on the myocardium. Intracoronary drug infusion also results in a small, but consistent decrease in heart rate. The decrease in heart rate is associated with a decrease in plasma noradrenaline, and appears to reflect a reflex withdrawal of sympathetic tone, which is presumably a consequence of improved left ventricular pump function.

**Vasodilator action of milrinone**

Although milrinone exerts a potent direct vasodilator effect in vitro, the relevance of this action to patients with congestive heart failure cannot be assumed. This issue has been approached directly by Cody et al., who evaluated the effect of a direct brachial artery infusion of milrinone on forearm blood flow measured by impedance plethysmography in patients with moderate to severe congestive heart failure. By infusing milrinone directly into brachial artery, it was possible to achieve therapeutic concentrations of milrinone in the forearm circulation, in the absence of significant drug accumulation. For example at brachial infusion rates of 10 and 20 ng µmin⁻¹ per 100 ml forearm volume, therapeutic milrinone concentrations of 223 and 298 ng ml⁻¹ were achieved in the forearm circulation, whereas there was no significant accumulation of drug in the systemic circulation. Thus, using this technique, Cody et al. were able to draw conclusions regarding the direct effect of milrinone on the forearm vasculature. Since infusion of milrinone into the brachial artery caused a significant increase in forearm blood flow and a significant decrease in forearm vascular resistance, it can be concluded that therapeutic levels of milrinone result in significant direct vasodilatation in patients with congestive heart failure.

We have used two approaches to evaluate the relative contribution of vasodilatation to the overall haemodynamic effect of milrinone in patients with...
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Figure 2  Haemodynamic effects of intracoronary infusion of milrinone at a rate of 50 μg min⁻¹ to 11 patients with congestive heart failure. HR, heart rate; MAP, mean arterial pressure (mmHg); SVR, systemic vascular resistance (dyn s cm⁻²); LVEDP, left ventricular end-diastolic pressure (mmHg); +dP/dt, left ventricular peak +dP/dt (mmHg s⁻¹); SVI, stroke volume index (ml beat⁻¹ m⁻²); SWI, stroke work index (g min⁻¹ m⁻²). (Reproduced, with permission, from reference 10.)

congestive heart failure. First, the haemodynamic effects of several doses of milrinone and nitroprusside were compared in the same group of patients with moderate to severe congestive heart failure. Under these circumstances, it was possible to match the infusion rates of milrinone and nitroprusside for similar reductions in arterial pressure and left ventricular end-diastolic pressure, thereby using nitroprusside to approximate the vasodilator effects of milrinone. The increase in the stroke work index caused by milrinone was significantly greater than that caused by nitroprusside. Thus, although vasodilatation could account for a substantial portion of milrinone's effect on the left ventricular pump function, it could not account for the entire action. The difference between nitroprusside and milrinone presumably reflects the positive inotropic action of the latter.

As a second approach to this issue, we compared the effects of intracoronary and intravenous milrinone infusion. In eight patients with moderate to severe congestive heart failure, intracoronary milrinone infusion (at a rate of 50 μg min⁻¹) was followed immediately by an intravenous bolus of milrinone (75 μg kg⁻¹). Since both routes of administration were predicted to result in therapeutic drug levels in the myocardium, we reasoned that the haemodynamic effect of intravenous drug would be a reflection of both the positive inotropic action and the vasodilator action of the drug, whereas the effect of intracoronary drug would reflect only the myocardial action. As anticipated, intracoronary administration of milrinone resulted in increases in left ventricular +dP/dt, and stroke volume and stroke work indices, and small decreases in right atrial and left ventricular end-diastolic pressures, whereas intracoronary drug caused no decrease in the mean arterial pressure or the systemic vascular resistance. Subsequent intravenous administration of milrinone produced substantial decreases in the mean arterial pressure and the systemic vascular resistance, further marked decreases in right atrial and left ventricular end-diastolic pressures, and further significant increases in stroke volume and stroke work indices (Fig. 3).

From this type of analysis, it appears that both the positive inotropic and vasodilator actions of milrinone contribute significantly to the drug's net haemodynamic effect. Precise quantification of the relative contributions of these two actions should be avoided, because it is unlikely that the experimental condi-
Figure 3  The comparative haemodynamic effects of intracoronary infusion of milrinone at a rate of 50 μg min⁻¹ (ICM) and the subsequent infusion of intravenous milrinone in a dose of 75 μg kg⁻¹ (IVM) to eight patients with congestive heart failure. (Reproduced, with permission, from reference 10.)

Reflex haemodynamic effects of milrinone

In congestive heart failure there is substantial activation of the sympathetic nervous system. The level of sympathetic nervous system tone is modulated by arterial baroreceptors, low-pressure receptors in the heart, and possibly, left ventricular receptors. Consequently, changes in heart size, pressure and/or function can affect the level of sympathetic nervous system activity, which, in turn, may indirectly affect vascular tone and/or myocardial performance. As noted previously, intracoronary milrinone infusion results in significant decreases in plasma noradrenaline and heart rate, presumably indicative of reflex sympathetic withdrawal. In order to evaluate the possible effect of reflex sympathetic withdrawal on vascular tone, we have studied forearm blood flow and venous capacitance by plethysmography during intracoronary milrinone infusion[14].

We found that intracoronary administration of milrinone, when infused at a rate that substantially improves left ventricular pump function, has no significant effect on forearm vascular resistance. However, venous capacitance, a measure of venous tone, is significantly increased, suggesting that indi-
rect venodilatation occurs. When the same patients subsequently receive intravenous milrinone, both forearm vascular resistance and venous capacitance change substantially, reflecting the direct effects of the agent. Thus, it appears that reflex sympathetic withdrawal due to the positive inotropic action of the drugs on the heart may result in a small degree of venous dilatation, which may contribute to the small decreases in left- and right-heart filling pressures observed during intracoronary drug infusion. This effect is overshadowed by the more potent direct vasodilator effects of the agent in clinical practice.

The vasodilator effects of milrinone appear to differ significantly from those of angiotensin-converting enzyme inhibitors such as captopril. LeJemtel et al.\[^{[15]}\] have compared the effects of milrinone and captopril, administered alone and together, on the systemic and regional haemodynamics of patients with moderate to severe congestive heart failure. Interestingly, they found that the haemodynamic improvement caused by the two agents was additive, so that the increase in stroke volume was greater with the two drugs together than with either agent alone. In contrast, they found that the regional blood flow effects of the two drugs were complementary. Captopril produced a substantial increase in renal blood flow, with relatively little change in leg muscular blood flow. Conversely, milrinone resulted in an improvement in leg blood flow when added to captopril, but appeared to have no further effect on renal blood flow. Thus, it may be anticipated that captopril will be most effective with regard to improving renal function, whereas in the short term, milrinone may be more effective with regard to improvement in exercise performance.

Conclusions

Milrinone differs significantly from pure inotropic or pure vasodilator agents. When compared to a pure vasodilator such as nitroprusside, milrinone exerts a greater haemodynamic effect, presumably reflecting its additional positive inotropic action. Clinically, this may allow milrinone to be tolerated by some patients whose response to vasodilators is limited by hypotension. Alternatively, milrinone’s vasodilator action may help to offset the potentially adverse effects of positive inotropic stimulation on myocardial energetics. For example, Monrad et al.\[^{[16]}\] and Grose et al.\[^{[17]}\] have compared the effects of dobutamine and milrinone on left ventricular pump function and myocardial oxygen consumption in patients with congestive heart failure. Although both agents improved left ventricular pump function to a comparable degree, dobutamine increased myocardial oxygen consumption, whereas milrinone had no effect, presumably reflecting the ability of milrinone to decrease left ventricular loading conditions which are an important determinant of myocardial oxygen demand. Because the regional vasodilator effects of milrinone differ significantly from those of captopril, it is likely that the combined administration of milrinone and an angiotensin-converting enzyme inhibitor may have clinically important advantages over the use of either agent alone.

References


Discussion

PROFESSOR W. BLEIFELD (F.R.G.)

A decrease in the left ventricular filling pressure could be due to a direct myocardial effect, but it could also be due to an improvement in systolic function. Could you outline what effect milrinone had upon end-diastolic volume and end-systolic volume?

DR W. COLucci

End-diastolic volume and end-systolic volume were not measured in this study. Using radionuclide methods, Monrad and co-workers found that the left ventricular volume was decreased by milrinone in some patients and increased in others. On average, there was no significant change in end-diastolic volumes.

PROFESSOR W. BLEIFELD (F.R.G.)

What is the clinical impact of the lusitropic effect of milrinone?

DR W. COLucci

It is difficult to assess the extent to which the lusitropic effect contributes to the reduction in filling pressure achieved by milrinone. However, this effect may be more important during exercise because of a heightening of the sympathetic tone.

PROFESSOR L. STORSTEIN (NORWAY)

Could you comment on the effect of milrinone on heart rate in patients with congestive heart failure?

DR W. COLucci

There is a dose-related effect on heart rate when the drug is given systemically, but in our study the heart rate was affected at higher doses than those that produced the inotropic effect. In studies using intracoronary administration the heart rate was reduced, and this was associated with a decrease in plasma levels of noradrenaline. Thus the improvement in pump function activates reflex mechanisms that cause withdrawal of sympathetic tone, leading to vasodilatation and a slowing of the heart rate.

DR SCHMIDT (F.R.G.)

Were arrhythmias observed following milrinone treatment?

DR W. COLucci

Arrhythmias did occur, but in the vast majority of patients there was no change in the level of complex or simple arrhythmias.

UNIDENTIFIED SPEAKER

Does milrinone act only on cardiac muscle or does it act on other smooth muscle? Is there a diuretic effect due to increased cardiac output and peripheral vasodilatation, and can milrinone be used in combination with diuretics?

DR W. COLucci

An improvement in overall pump function is probably due to effects on both cardiac muscle and vascular smooth muscle. Diuretic effects have been observed, probably due to an increased cardiac output resulting in increased renal blood flow. However, there may even be a tendency to retain some salt and water due to peripheral non-selective vasodilatation. Diuretic requirement should be re-evaluated after therapy.

UNIDENTIFIED SPEAKER

Did the patients in your study receive a diuretic in addition to treatment with milrinone?

DR W. COLucci

All the patients studied had previously been on diuretics for some time as well as vasodilators. Indeed, most patients had been treated with digitalis, diuretics and angiotensin-converting enzyme inhibitors before the study. As all the patients would be expected to have a strong tendency to retain sodium, it was not thought advisable to withhold diuretics.