European Heart Journal (1983) **4** (*Supplement D*), 129–135

Practical guidelines for treatment with beta-blockers and nitrates in patients with acute myocardial infarction

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Treatment of a patient with myocardial infarction might include opiates and sedatives to reduce pain and anxiety, heparine, antiarrhythmic drugs, diuretics which aim at improvement of myocardial function and drugs which might reduce the ischemic area at risk and thus mortality such as beta-blockers, vasodilators and possibly calcium antagonists. Obviously a selection of these and other therapeutic agents should be made for each individual patient. Guidelines for such a selection are presented in this paper. These are based on assessment of the hemodynamic state in a given patient: heart rate, blood pressure and presence or absence of heart failure as determined by non-invasive examination or by hemodynamic monitoring with a pulmonary artery catheter.

An attempt should be made to reach an optimal hemodynamic state quickly, preferably within one hour of admission to the coronary care unit: a heart rate between 60 and 80 b.p.m., a systolic blood pressure between 100 and 140 mmHg and absence of signs of heart failure. For this purpose fast-acting intravenous drugs should be employed. Possibly myocardial preservation could also be achieved by prompt recanalization of an occluded coronary artery. At present, however, this is still an experimental procedure which should be further investigated.

Treatment of patients with acute myocardial infarction can be approached in different ways. The classical approach is *symptomatic*. Symptomatic treatment includes reduction of pain and anxiety, and treatment of life-threatening arrhythmia's or pump failure when such conditions are recognized[1].

More recently *prophylactic treatment* has been proposed. This includes heparine to prevent deep vein thrombosis, pulmonary embolism and possibly intraventricular thrombosis[1], and lidocaine to prevent ventricular fibrillation[2]. Furthermore beta-blockers or nitrates can be administered in order to limit infarct size and prevent complications of myocardial infarction[3–6]. As discussed by others in this supplement[3,4], indications for beta-blockers in acute myocardial infarction are still uncertain, as well as indications for prophylactic use of nitroprusside and nitroglycerine[7,8]. Even if further ongoing studies demonstrated that beta-blockers, nitrates and possibly calcium antagonists do indeed improve prognosis after myocardial infarction, the physician still faces the question of which drugs should be given to a particular patient and in what doses. Should all patients then be treated prophylactically with heparine, lidocaine[2], nitroprusside[6], a beta-blocker[9] and a calcium antagonist?

Later contributions to this supplement address themselves to these problems. In our opinion, the best solution to the above question would be a *physiological approach*, based on an understanding of the development of myocardial infarction and its complications (Table 1).

Myocardial ischemia is the key factor in the pathophysiology of an evolving myocardial infarction. Ischemia causes pain and anxiety, while anxiety can increase the myocardial demand through an enhanced sympathetic drive. The contractile function of myocardial cells is impaired by ischemia, while prolonged ischemia results in permanent loss of myocardial tissue. The increased filling pressure and increased end-diastolic volume which are the results of myocardial ischemia can reduce coronary blood flow and increase myocardial oxygen demand. Finally ischemia is the direct cause of life-threatening arrhythmias which occur in some of these patients.

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0195–668X/83/04D129+07 $02.00/0

Table 1 Treatment of myocardial infarction can be approached according to three principles which address specific issues as indicated in the table

Symptomatic	Prophylactic	Physiological
Pain, anxiety	Preservation of myocardial function	Restoration of O_2 balance
Heart failure		
Arrhythmias	Prevention of complications	Optimal hemodynamics

In our experience prophylactic treatment with lidocaine, although effective[2] is not mandatory. Ventricular fibrillation occurs infrequently and unpredictably in patients admitted with myocardial infarction, and can most often be converted by prompt electroshock. In 1981 364 patients with myocardial infarction were treated at our coronary care unit. Hospital mortality was 13%. Primary ventricular fibrillation was irreversible in only two patients. The most frequent cause of death was pump failure in 36 patients (Table 2). The keystone of treatment of myocardial infarction should be the prompt removal of all factors which excessively enhance myocardial oxygen consumption and, where possible, prompt restoration of myocardial blood flow.

In this paper practical guidelines are presented for the treatment of myocardial ischemia and left ventricular failure in patients with acute myocardial infarction. These guidelines have been developed for studies of the effect of intracoronary thrombolysis in acute myocardial infarction which are currently ongoing in several centers in the Netherlands[10–13].

Reduction of myocardial oxygen demand

Nitrates, beta-blockers and calcium antagonists can be used for the reduction of myocardial oxygen demand. Since the mechanism(s) of action of these three classes of drugs are different, they may be combined to achieve optimal effect. However, the precise interactions of these three classes of drugs are uncertain in acute infarction and few data are available to optimize the dosage of these drugs in an individual patient

Beneficial effects on infarct size and hospital mortality have been documented for both nitroprusside[6] and nitroglycerine[5] provided that these drugs are given during the first hours of an evolving infarction. Late administration of nitroprusside[7] did not improve patient survival[8]. Since the major effects of nitrates are a reduction of left ventricular filling pressure (preload) and arterial pressure (afterload), it seems that mostly patients with heart failure and hypertension will benefit from such drugs. The question then remains, to what levels afterload and preload should be reduced to achieve optimal reduction of myocardial ischemia. Unfortunately this question was not addressed in depth in previous studies[5–8]. We would aim for a mean arterial pressure between 90 and 100 mmHg or a systolic arterial pressure between 100 and 140 mmHg. If signs of left ventricular failure are present, the dosage of nitrates can usually be increased up to 150–200 $\mu g\ min^{-1}$ for both nitroglycerine and nitroprusside. When a Swan-Ganz catheter is used for hemodynamic monitoring we would aim for a left ventricular filling pressure between 5 and 10 mmHg. The studies with beta-blockers in acute myocardial infarction have been summarized by Hampton[4]. The results of the two large studies with metroprolol[9] and alprenolol[14] indicate that reduction of infarct size and mortality can be achieved when these drugs are administered within the first hours of infarction. Unfortunately these reports again fail to indicate specific subgroups of patients who benefit most from such treatment. More recent analysis of the data from the metoprolol trial indicate that the reduction of mortality was apparent only if heart rate upon admission was higher than 70/min before administration of metoprolol[15]. No serious side-effects were observed in patients with mild left

Table 2 Admissions and hospital mortality at the coronary care unit of the Thoraxcenter in 1981

Total admissions		1360
Myocardial infarction		364 (27%)
Infarction mortality		
shock	36	
rupture	6	
primary VF	2	48 (13%)
block	2	
unknown	2	
Other mortality	18	

ventricular failure. However, it is not clear whether a drug with a negative inotropic effect would be beneficial to such patients. Therefore we would propose to administer beta-blockers only in patients with heart rates above 80 b.p.m. and in patients with hypertension, provided that no signs of left ventricular failure are apparent. We would titrate the dosage such that heart rate would remain between 60 and 80 b.p.m. and systolic blood pressure above 100 mmHg.

So far, large scale studies with calcium antagonists in acute myocardial infarction are not available. However, animal studies indicate preservation of myocardial function after verapamil[16], nifedipine[17] and diltiazem[18]. At present we would use calcium antagonists in patients with prolonged chest pain and ECG changes as a sign of prolonged and persistent myocardial ischemia, particularly in patients in whom beta-blockers are contraindicated or when beta-blockers have no sufficient effect.

Selection of treatment in specific patient groups

Selection of the appropriate mode of treatment can be based on classification of the hemodynamic state of a particular patient. Optimal classification and titration of dosages can be achieved by careful hemodynamic monitoring. However, in patients without signs of hemodynamic impairment adequate treatment can be begun without invasive measurements. In Table 3 a set of rules for hemodynamic classification is summarized. These are based on the MIRU classification[19], which has been developed from the earlier Killip[20] and Norris[21] classification systems. Details on hemodynamic classification have been presented by Forrester *et al.*[22] and Wolfenbuttel *et al.*[23] elsewhere. Obviously classification schemes such as that presented in Table 3 are oversimplified. Often a patient has characteristics which belong to various classes. The classification should then be based on the predominant findings. In order to ascertain how frequently the various conditions, shown in Table 4, do occur, hemodynamic data were analyzed from 200 consecutive patients treated for myocardial infarction at the Thoraxcenter. Of these 200 patients 55% had no signs of heart failure (MIRU class I), 22% showed mild left ventricular failure (MIRU class II) and 23% suffered from severe failure or shock. In Table 5 the percentages of patients in the hemodynamic subsets of class I and II are presented.

When the guidelines in Table 4 are applied, 19%

Table 3 Hemodynamic and clinical classification of patients with acute myocardial infarction. Many patients exhibit a combination of features of more than one class. These can be classified according to the dominant characteristics.

	Unit	Hyperdynamic*	Normal	Mild failure	Frank failure†	Shock†
Heart rate	b.p.m.	> 80	60– 80	80–100	90–110	> 110
MAP	mmHg	> 100	90–100	80– 90	60– 80	< 60
LVFP	mmHg	< 12	<12	12– 16	16– 20	> 20
Cardiac Index	L/min/m^2	> 40	3·0–4·0	2·5–3·0	2·0–2·5	< 2·0
SWI	gm/m^2 BSA	>4000	3000–4000	1200–3000	1200–2000	<1200

	Hyperdynamic	Normal	Mild failure	Frank failure	Shock
Mental state	anxiety	normal	tense	anxiety	restless
Skin	dry, warm	dry, warm	warm	cool	clammy
Pulse	normal	normal	normal	weak	very weak
Lungs	clear	clear	basal rhonchi	rhonchi	lung edema
Heart sounds	normal	normal	S_3?	S_3+S_4	S_3+S_4
Urine	> 50 ml/h	> 50 ml/h	40–50 ml/h	20–40 ml/h	< 20 ml/h

*A subset of patients suffers from hypovolemia, LVFP < 5 mmHg.
†Right ventricular infarction may cause hypotension and tachycardia with elevated central venous pressure and low LVFP.

Table 4 Guidelines for treatment of patients with myocardial infarction based on hemodynamic classification through combination of heart rate, blood pressure and signs of heart failure. An attempt should be made to achieve the optimal hemodynamic state soon after admission through prompt administration of appropriate short-acting intravenous drugs.

mmHg	Heart rate		
Systolic pressure	< 60	60–80	> 80
A. *No signs of left ventricular failure (MIRU I. KILLIP I)*			
> 140	atropine nitroprusside (pacemaker)	nitroprusside	beta-blocker nitroprusside
100–140	atropine (pacemaker)	—	beta-blocker
< 100	atropine volume exp. (pacemaker)	volume exp.	volume exp.
B. *Mild left ventricular failure (MIRU II, KILLIP II)*			
> 140	atropine nitroprusside (pacemaker)	diuretics nitroprusside	diuretics nitroprusside
100–140	atropine (pacemaker)	diuretics	diuretics
< 100	atropine dobutamine (pacemaker)	diuretics dobutamine	diuretics dobutamine
C. *Frank left ventricular failure or shock*			
> 140	atropine pacemaker nitroprusside	diuretics nitroprusside	diuretics nitroprusside
100–140	atropine pacemaker (nitroglycerine)	diuretics nitroglycerine	diuretics nitroglycerine
< 100	pacemaker dobutamine IABP	diuretics dobutamine IABP	diuretics dobutamine IABP

Table 5 Incidence of various hemodynamic subsets of patients as used in Table 4 assessed from data from 200 consecutive patients with myocardial infarction who underwent hemodynamic monitoring. No failure was present in 55% of patients, mild failure in 22% and severe failure or shock in the remaining 23%. The latter group is not included in the table. Beta-blockers might be used in 19% of patients without failure, with normal or elevated blood pressure and with heart rate greater than 80/min. Nitroprusside might be given in 15% of patients with elevated blood pressure. Volume expansion might be used in 6% of patients with hypotension without heart failure. Diuretics might be used in 21% of patients with mild failure without bradycardia.

	% Patients in each hemodynamic subset							
	No failure 55%				Mild failure 22%			
Systolic P		< 60	60–80	> 80	HR	< 60	60–80	> 80
	> 140	—	5	5		—	2	3
	100–140	5	20	14		1	6	10
	< 100	1	4	1		1	—	—

of the patients should be treated with a beta-blocker and 15% of the patients with nitroprusside or possibly nitroglycerine. In addition some 10% of the patients who are in severe failure (class III) should obviously be treated with nitrates or other vasodilating drugs. Those in shock should be assessed early and treated with mechanical support such as the intra-aortic balloon pump or corrective surgery.

Initiation and discontinuation of treatment

The goal of treatment as discussed above is the reduction of myocardial ischemia and, hopefully, preservation of myocardial function. Therefore the aim should be an immediate correction of hemodynamic abnormalities if present. The pain related elements can be corrected by intravenous administration of sedatives (morphine, heroin, fentanyl, doperidol, diazepam). The optimalization of cardiac function during ischemia is achieved with beta-blockers (e.g. metoprolol), diuretics (furosemide, etacrynic acid, bumetanide), and vasodilators (nitroprusside, nitroglycerine or calcium antagonists). In most patients the desired hemodynamic condition can be reached within one hour. Thus, fast-acting drugs are preferred and therapy should be intravenous. In patients who have already received beta-blockers, nitrates and calcium antagonists before the development of an infarct, these drugs should be continued unless adverse effects such as bradycardia, hypotension or heart failure occur. Between 24 and 48 hours after the onset of infarction, most drugs can gradually be withdrawn, or replaced by longer-acting drugs which can be given orally. It has been shown that prolonged administration of beta-blockers can improve prognosis in part of the patients. Again, these studies have not addressed the selection of subgroups of patients who benefit most from such treatment. From other investigations[24] it is known that patients with single vessel disease or patients without signs of ischemia after myocardial infarction and a normal exercise tolerance, have a very low risk of recurrent infarction or death. It is unlikely that such patients need any prophylactic therapy. Therefore we propose to withdraw beta-blockers as well as nitrates and calcium antagonists after the first few days. These drugs are to be continued or restarted in patients with hypertension, angina, or ECG signs of ischemia during a pre-discharge stress test[24]. Others would prescribe a beta-blocker to most post-infarct patients unless contraindications are presented or side-effects occur[9,15].

Restoration of myocardial blood flow

Recently studies by Rentrop[25] and others[26] have confirmed that myocardial infarction is associated with occlusion of a major coronary artery in approximately 85% of patients. The occluding thrombus can be dissolved in 70–90% of patients if streptokinase is administered in the occluded coronary artery[10,25,26] within the first 4–6 hours after the onset of chest pain. This approach may restore myocardial blood flow and thus preserve myocardial function. Several case reports have documented reversal of cardiogenic shock after successful thrombolysis[27]. At the Thoraxcenter a randomized trial is presently underway, comparing intracoronary streptokinase with conventional therapy[10–12]. Preliminary data indicate that preservation of myocardial function can be achieved if intracoronary thrombolysis is begun within 4 hours after the onset of myocardial infarction (Table 6). However, the precedure is certainly not without risk[10], and so far one-year survival has not been improved (Table 7). It is our opinion that intracoronary thrombolysis is still an experimental procedure[26] which should be evaluated in large randomized trials. At present the cornerstone of treatment of myocardial infarction remains prompt

Table 6 Preliminary data during cardiac catheterization 2 weeks after admission in patients with acute myocardial infarction who participated in a randomized trial on intracoronary thrombolysis with streptokinase. Data were collected in 51 patients out of the first 71 who enrolled in the study. The other 20 patients refused angiography (17) or died prior to the investigation (3). The infarct-related coronary vessel (IRV) was patent at control angiography in 9 patients from the control group (35%) and in 22 patients treated with streptokinase (88%). Patients treated with streptokinase had a lower end diastolic volume and a greater ejection fraction than the controls ($P < 0{\cdot}05$, t-test). Baseline characteristics of the two groups at admission were similar.

	Controls		Streptokinase
Heart rate	84 ± 20		75 ± 13
Mean art P.	92 ± 16		97 ± 15
LVEDV	101 ± 30	**	83 ± 15
Ejection Fr.	43 ± 17	**	56 ± 10
Cardiac index	$3{\cdot}3 \pm 1{\cdot}1$		$3{\cdot}4 \pm 0{\cdot}7$
IRV patency	9/26		22/25

Table 7 Preliminary follow-up data from 98 patients enrolled in the randomized trial on intracoronary thrombolysis at the Thoraxcenter, October 1982. Follow-up ranged from 1 to 18 months, median 9 months. Fifty-one patients were allocated to streptokinase treatment (N) and 47 were controls. Of the 51 patients, 5 refused the intervention (Ref.), 9 had an open infarct-related vessel at acute angiography (○→○) and 37 had an occluded artery. In 7 patients the artery remained occluded (●→●), and in 30 recanalization was achieved (●→○). Twelve out of these 30 patients underwent PTCA immediately after thrombolysis. At present, no differences are apparent in mortality, reinfarction or late PTCA or bypass surgery between the two groups.

	Controls	Streptokinase					
	N	Ref.	●→●	●→○	●→○ +PTCA	○→○	
Patients	47	51	5	7	18	12	9
Death	3	8	2	2	3	—	1
Reinfarction	3	5	2	—	2	—	1
Late CABG/PTCA	12	9	—	2	4	—	3

correction of anxiety, pain, ischemia and arrhythmias and the direction towards an optimal hemodynamic state in each patient by proper selection of approaches as discussed in this paper.

Unresolved problems

It remains uncertain which dosage of beta-blockers, calcium antagonists and nitrates should be given to patients with established myocardial infarction. In our view such decisions should be based mainly on the assessment of the hemodynamic state of a given patient. However, there is no proof that the physiological approach presented in this paper is optimal in terms of preservation of cells threatened by ischemia. Controversy remains even on the choice of a specific drug within a given class such as the selection between nitroglycerine and nitroprusside, or between various types of beta-blockers[28]. Further systematic studies in patients with documented myocardial infarction are mandatory to solve such questions. We recommend that such studies employ measurements which can be used to identify those patients who will benefit most from such interventions.

The guidelines for treatment of patients with myocardial infarction have been developed by the working group for a multicenter trial of intracoronary thrombolysis in The Netherlands. This trial is sponsored by the Inter University Institute of Cardiology. Members of the working group were J. P. Roos, P. J. de Feyter and J. Res, Department of Cardiology, Free University Amsterdam; R. W. Koster, Department of Cardiology of the Amsterdam Medical Center; J. J. R. M. Bonnier, H. R. Michels and F. van Rey, Department of Cardiology, Catharina Hospital Eindhoven; X. H. Krauss and P. Remme, Department of Cardiology Zuiderziekenhuis Rotterdam and the authors of this paper.

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