European Heart Journal (1999) **20,** 83–84
Article No. euhj.1998.1320, available online at http://www.idealibrary.com on IDEAL

Editorials

Modifying breathing patterns in chronic heart failure

Introduction

Chronic heart failure is now recognised as a multisystem syndrome[1] with a variety of pathophysiological abnormalities including, in addition to ventricular dysfunction, alterations in skeletal muscle metabolism, peripheral blood flow and endothelial, respiratory, autonomic, and neurohumoral functions, which all contribute to reduce exercise tolerance and generate symptoms. Accordingly, the treatment of heart failure should also embrace non-cardiac factors, and in particular non-pharmacological measures.

The benefits of exercise training[2] include an increase in exercise tolerance and a decrease in abnormal hyperventilation on exercise by reducing the ventilation/CO_2 ratio. Other benefits are an increase in peripheral blood flow at peak exercise, improvement in skeletal muscle metabolism, reduction of sympathetic overactivation, increased vagal activity and baroreflex sensitivity, and reduction of chemoreflex overactivation. Exercise training is probably effective as a result of reversing the physical deconditioning secondary to prolonged physical inactivity[1,2].

In addition to physical training other strategies have successfully reduced respiratory disorders in heart failure. These disorders include reduced diffusion capacity and impaired ventilation/perfusion ratio. Abnormalities in the ventilatory pattern are also frequent and lead to frank Cheyne–Stokes respiration, which has adverse prognostic significance[3]. Unstable ventilatory patterns cause low and unstable oxygen saturation, with a consequent increase in sympathetic activity and a further increase in oxygen demand. Finally, general physical deconditioning also affects lung musculature, thus decreasing the ability to maintain adequate ventilation during exercise, and is a possible source of the symptom of dyspnoea[4]. Physical training[4], selective training of respiratory muscles and reduction of ventilatory work improve ventilation dynamics and exercise performance[5,6]; Cheyne–Stokes respiration can be partly corrected by oxygen delivery[7] or by continuous nasal positive airway pressure[8].

Our study in brief

We analysed the spontaneous breathing pattern of 50 subjects with heart failure and 15 healthy controls, and evaluated the impact of breathing at different rates[9].

A large group of heart failure subjects showed reduced oxygen saturation at rest, independent of spontaneous Cheyne–Stokes respiration. Respiration at controlled frequency markedly reduced respiratory instabilities and abolished Cheyne–Stokes respiration. In addition, controlled breathing increased oxygen saturation; slower breathing rates (6 and 3 breaths . min^{-1}) were as equally effective as higher rates (15 breaths . min^{-1}) in increasing oxygen saturation, while minute ventilation remained unchanged at 6 breaths . min^{-1} and even decreased at 3 breaths . min^{-1}, compared to spontaneous breathing, whereas it increased at 15 breaths . min^{-1}. Slower breathing also improved indirect indices of ventilation/perfusion and alveolar ventilation, thus proving more efficient.

In the second part of the study we taught subjects this pattern as part of their spontaneous breathing. Subjects practising yoga or transcendental meditation tend to have slower (and deeper) spontaneous respiration[10]. In addition, yoga exercises lead to a highly refined skill, that of controlling respiration and coordinating respiratory muscles. While teaching a full yoga programme to our heart failure subjects was beyond our purpose and possibilities, the subjects were taught a yoga-derived type of respiration, the so-called 'complete yogic breathing'. This requires mobilization in sequence (within the same breath) of the diaphragm, then the lower and finally the upper chest, during inspiration, and the same during expiration, with resulting slow and deep breathing, which spontaneously tends to a frequency in the range of 6 min. During the first month nine subjects trained (guided by a physiotherapist in hospital) at home, for about 1 h (either continuous or split into shorter periods), every day during the study. Six subjects (control group) performed no training.

The trained subjects showed a small but significant increase in exercise performance and a

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decrease in the perception of dyspnoea during exercise, in addition to increased resting oxygen saturation, with no changes in the control group. One month after the completion of the training these results were still evident.

The trained subjects reduced their resting breathing rate. Although extreme care was taken not to influence the subjects' spontaneous attitude (measurements were taken when the subject was unaware of it), awareness of the training goal might have influenced the 'spontaneous' pattern during recordings.

Similar to other types of training, the results are critically dependent upon the motivation of the patient to undertake and maintain the commitment to continue the practice. The motivation to perform this training increased during the study, thus indicating that the task appeared not only feasible but also worthwhile, from the point of view of the patients.

Comments and implications

In heart failure, even normal daily tasks stress patients close to the limits of their cardio-pulmonary exercise reserve. Therefore, even modest improvements in the ability to perform exercise would provide substantial benefits and improve quality of life.

Thus, although the extent of the improvement found in our study after 1 month of respiratory-pattern training is about half that obtained with physical training[2], it might still be of interest in view of the improvement in dyspnoea and fatigue during exercise, particularly since it did not involve any physical exercise and was strictly limited to the respiratory pattern. On the other hand, although general physical training might also improve this aspect of respiration, this is not specifically considered in current training protocols[2].

This respiratory-pattern training results, at least, in better coordination of the respiratory muscles and of the diaphragm, and a greater facility to slow down the breathing rate, regardless of whether it permanently modifies the spontaneous breathing habit. This completely different approach might thus potentiate the results obtained with other rehabilitation programmes available today; alternatively, it might still represent an option when other forms of training are not available or practical, as in more advanced stages of disease.

The present study was carried out in a limited number of subjects and for a total observation of only 2 months. Therefore the long-term efficacy and applicability of this training should be demonstrated. Nevertheless, the increase in motivation to continue this training indirectly suggests that the subjects found it at least easily tolerable, and, with continuing practice, worthwhile.

In conclusion, we found that simple training to improve breathing pattern gives additional benefit, both in symptoms and exercise capacity, when added to conventional therapy, in this complex syndrome of heart failure.

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References

[1] Coats AJS, Poole-Wilson PA. The syndrome of heart failure. In: Weatherall DJ, Leadingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. Oxford, UK: Oxford University Press, 1995: 2228–38.
[2] Piepoli M, Flather M, Coats AJS. Overview of studies of exercise training in chronic heart failure: the need for a prospective randomized multicentre European trial. Eur Heart J 1998; 19: 830–41.
[3] Mortara A, Sleight P, Pinna GD, Maestri R, Prpa A, La Rovere MT. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. Circulation 1997; 96: 246–62.
[4] Davey P, Meyer T, Coats AJS *et al*. Ventilation in chronic heart failure: effects of physical training. Br Heart J 1992; 68: 281–3.
[5] Mancini D, Henon D, La Manca J, Donchez L, Levine S. Benefit of selective respiratory muscle training on exercise capacity in patients with chronic congestive heart failure. Circulation 1995; 91: 320–9.
[6] Mancini D, Donchez L, Levine S. Acute unloading of the work of breathing extends exercise duration in patients with heart failure. J Am Coll Cardiol 1997; 29: 590–6.
[7] Staniforth AD, Kinnear WJM, Starling R, Hematski DJ, Cowley AJ. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne–Stokes respiration. Eur Heart J 1998; 19: 922–8.
[8] Naughton MT, Liu PP, Benard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne–Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 1995; 151: 92–7.
[9] Bernardi L, Spadacini G, Bellwon J, Hajric R, Roskamm H, Frey AW. Influence of breathing frequency and pattern on oxygen saturation and exercise performance. Lancet 1998; 351: 1308–-1311.
[10] Stanescu DC, Nemery B, Veritier C. Marecal C. Pattern of breathing and ventilatory response to CO_2 in subjects practicing hata-yoga. J Appl Physiol 1981; 51: 1625–9.

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The ultimate follow-up

See page 136 for the article to which this Editorial refers

Most treatments for heart failure are gauged against whether they reduce mortality. Several have passed that test, most notably the angiotensin converting enzyme inhibitors (ACEIs), beta-blockers and most recently spironolactone (the RALES trial). The pace of change is such that definite evidence for the last two comes to date only from press releases from studies stopped early (CIBIS-II, RALES) or oral presentations with the formal papers eagerly awaited. Whilst this is mark of success for the heart failure research community as it establishes clearly effective strategies, a reduction in mortality is often not easy for patients to understand and difficult for them to factor into decision-making for any treatment that is difficult or which entails unpleasant side-effects. What patients often want to know is how much extra life the treatment is likely on average to produce. Trials usually are presented either as a risk reduction, or more recently numbers of patient years of treatment needed for each life saved, not in terms of average life prolongation. The reason for this is that they are stopped when only a minority of deaths in participating patients have occurred and the extent of life prolongation for the average patient cannot be accurately estimated.

The original Co-operative North Scandinavian Enalapril Survival Study (CONSENSUS) was the first randomized controlled trial in heart failure to demonstrate a convincing and statistically robust answer for mortality reduction with a medical treatment[1]. As such it will remain a classic paper in the medical literature. The present issue of the journal contains another first, a long-term follow-up of the same trial, in this case the first trial in heart failure to have virtually universal follow-up of all patients enrolled to death[2]. It can thus tell us many things previously unattainable. It can tell us the mean, median and range of survival of a large cohort of well-defined patients with severe heart failure, it can tell us the effects of a delay in introduction of this effective treatment and it can tell us the true average life prolongation for the treatment under study.

The original CONSENSUS study was stopped on the advice of the Safety Committee on 14 December 1986, and the present report details a 10-year follow-up of all patients alive at the termination of the orginal study. Of the original 253 randomized patients one patient only was lost to follow-up and there were five long-term survivors (all in the original enalapril group). Thus there is complete survival data on 97·6% of patients enrolled. Overall risk reduction for being randomized to enalapril instead of placebo was 30% (95% CIs 11–46%), despite the trial being terminated with all patients recommended to go onto open label enalapril after a treatment period of only 6 months on average.

Several important points emerge: (1) the beneficial treatment effect of 6 months enalapril continued for up to another 3·5 years; (2) the average life increment was 260 days, extending survival time by 50% from 521 days to 781 days; and (3) even in the non-randomized follow-up period those who did actually receive and ACEI fared better than those who did not.

It is worth dwelling on some of these numbers. The results are not pure because the original randomization schedule was obviously not adhered to after the trial was stopped on ethical grounds, and there was still a small number of patients alive even at 10 years (at under 3% they would distort average survival times and hence median or percentile life increments are preferable measures of effectiveness). However, even with these reservations it is instructive to allow some thinking and estimating about what the trial numbers might mean. If we assume that the true long-term placebo survival rate could be estimated by hypothesizing that all patients originally randomized to placebo would continue with the same progressive mortality as during the first 6 months of the trial, we would estimate that all patients would have been dead by 18 months (extrapolating the randomized phase placebo survival curve to 100% mortality). This is the worst case scenario for the placebo group. In fact >90% mortality was seen at between 2–3 years in the group originally randomized to placebo who did not cross over to enalapril when the trial was stopped (taken from Fig. 3). The best case scenario for the original enalapril group is that seen for those randomized to enalapril who continued on treatment after original study closure. This group reached a 90% mortality rate at about 4·5 years, giving a most optimistic incremental survival of a maximum of 3 years and an approximate average of 18 months (an eyeball estimate from Figs 1 and 3). Thus we can estimate that in class IV patients, enalapril *given for 6 months* increases life expectancy by approximately 260 days (the result of this report), and *when given long-term* by 18 months (with an upper estimate of 3 years). Whilst this is welcome it is not the 'cure' for

heart failure that the headline mortality reduction from the original study might have been interpreted as showing. It also demonstrates how appalling the prognosis of class IV heart failure is, even with the best of contemporary medical care.

There will probably be very few 'complete' follow-up trials in the cardiological literature in the future (the lileal resection treatment for hyperlipidaemia trial, POSCH owing to its virtual absence of cross-overs could be one in the future[3,4]), and as a result this report is likely to be one of the classics of the heart failure literature and I predict its survival curves will become some of the most shown Kaplan–Meier curves in the cardiological community.

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References

[1] The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study. N Engl J Med 1987; 316: 1429–35.

[2] Swedberg K, Kjekshus J, Snapinn S, for the CONSENSUS-investigators. Long-term survival in severe heart failure in patients treated with enalapril — Ten year follow up of CONSENSUS I. Eur Heart J 1999; 20: 136–9.

[3] Buchwald H, Fitch L, Varco RL. Surgical intervention in atherosclerosis: partial ileal bypass and the Program on Surgical Control of the Hyperlipidemias (POSCH). Pharmacol Ther 1985; 29: 93–109.

[4] Buchwald H, Varco RL, Boen JR, *et al.* Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. Arch Intern Med 1998; 158: 1253–61.

European Heart Journal (1999) **20,** 86–88

Magnesium treatment in acute myocardial infarction: an unresolved consensus

See page 111 for the article to which this Editorial refers

Evidence from experimental studies, suggesting that magnesium has a beneficial effect in the setting of acute myocardial infarction, and the promising results of many small scale clinical trials, have always excited physicians, who are enthusiastic to find a magic remedy to prevent mortality from myocardial infarction.

Although the major meta-analysis of magnesium treatment in myocardial infarction was consistent with the trend of the experimental studies and supported the results of the individual clinical trials, concluding that 'magnesium treatment represented an effective, safe, simple and inexpensive intervention that should be introduced into clinical practice without further delay', the results have not received wholehearted acceptance due to the nature of the analysed data[1].

The two major trials, namely LIMIT-2 and ISIS-4 have revolutionized the issue of magnesium treatment in acute myocardial infarction, although the results of both trials were not consistent[2,3]. In contrast to animal studies and small scale trials of magnesium treatment (possible publication bias of positive results) showing a significant suppression of arrhythmias, LIMIT-2 and ISIS-4 did not show a clear-cut benefit in this regard. Limit-2 demonstrated some mortality reduction; however, in ISIS-4 there was no evidence of any beneficial effect of magnesium, even after the analysis of multiple subgroups. Interestingly, the LIMIT-2 authors tended to explain the mortality benefit from magnesium by mechanisms other than arrhythmia suppression. Both studies have been subject to many controversies. The discrepancy between the results has been ascribed to the timing of the magnesium administration and its relation to thrombolytic therapy. Magnesium was typically administered after the initiation of thrombolytic therapy in ISIS-4, whereas magnesium was given prior to a thrombolytic agent in LIMIT-2. It has been thought that the presence of magnesium protects the myocardium against reperfusion injury and this has been supported by experimental animal data[4].

In a well conducted study in this issue Parikka *et al.*[5] reported that magnesium treatment in the early phase of acute myocardial infarction resulted in suppression of ventricular arrhythmias and decrease

in QT dispersion. The authors suggested a pathophysiological link between magnesium treatment, decreased QT dispersion and decreased incidence of ventricular arrhythmias. In fact this interesting observation may reflect several electrophysiological effects of magnesium at the cellular level. It is well known that magnesium, being an essential co-factor for Na-K ATPase, has a modulating effect on mechanisms which control cellular potassium movements. Therefore magnesium deficiency may lead to loss of intracellular potassium, increased intracellular sodium and enhanced cellular excitability, and magnesium treatment may operate via potassium. These observations have been supported by a clinical study demonstrating the normalization of QT dispersion by intravenous potassium[6]. There is evidence, on the other hand, of a low myocardial level of magnesium in patients with ischaemic heart disease who died of acute myocardial infarction[7]. In a recent study Haigney *et al*.[8] demonstrated that even in the absence of drug therapy, experimental heart failure resulted in both tissue and cardiac loss of magnesium, possibly contributing to abnormal repolarization in heart failure. Furthermore, one clinical study showed that magnesium prevented an increase in action potential duration and prolongation of membrane repolarization, which normally occurs in ischaemic myocardium[9]. However, monophasic action potential recordings demonstrated that QT interval dispersion was an indirect measure of the heterogeneity of ventricular repolarization.

Increased QT dispersion, as a reflection of heterogeneity in ventricular repolarization, constitutes an electrophysiological substrate for re-entrant ventricular arrhythmias. However, it may not be easy to create a link between decreased QT dispersion and the frequency of ventricular premature beats and non-sustained ventricular tachycardia, which are supposed to originate from enhanced excitability. In an earlier report, Endoh *et al*.[10] could not show any correlation between QT dispersion and premature ventricular couplets after thrombolytic therapy and concluded that the mechanism of decrease in the frequency of premature ventricular couplets could not be explained by the reduction of QT dispersion. The present study also carries the common limitation of the previous reports: not all the patients had thrombolytic therapy and the temporal relationship between the thrombolytic and magnesium administration and arrhythmogenecity has not been clarified.

The suppression of arrhythmias of enhanced excitability origin might be explained partially by magnesium protection exerted on reperfusion injury, or many other cellular mechanisms mentioned in the present report may play a role. However, this argument does not exclude the antiarrhythmic potentiality of QT dispersion reduction, although it is not also easy to conclude that re-entrant arrhythmias could be prevented by magnesium therapy. Since the present study is not powered to be a prognostic study it is also not possible to predict the clinical significance of the arrhythmia suppression on mortality. It is well known that QT dispersion at discharge (not during the very early days) is predictive of susceptibility to later life-threatening ventricular arrhythmias and sudden death. In the present study the effect of magnesium therapy has been shown to be prolonged up to one week. However, I think it may still not be possible to make any clinical extrapolation about the prognostic significance of reduced QT dispersion by magnesium from this data.

In conclusion, being a major intracellular cation, magnesium can protect the myocardium against ischaemia-induced electrical instability in several different ways, including by the prevention of reperfusion injury or as demonstrated by Parikka *et al*.[5] by improving the heterogeneity of repolarization as expressed by reduction in QT dispersion. However, since the clinical data is still conflicting and due to the results of large trials such as ISIS-4, clinical extrapolation should be made carefully. On the available data routine intravenous magnesium administration is not recommended after acute myocardial infarction.

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References

[1] Horner SM. Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality. Meta analysis of magnesium in acute myocardial infarction. Circulation 1992; 86: 774–9.
[2] Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: Results of second Leicester Intravenous Magnesium Intervention Trial. Lancet 1992; 339: 1553–8.
[3] ISIS-4 Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet 1995; 345: 669–85.
[4] Christensen CW, Rieder MA, Silverstein EL, Gencheff NE. Magnesium sulphate reduces myocardial infarct size when administered before but not after coronary reperfusion in a canine model.Circulation 1995; 92: 2617–21.
[5] Parikka H, Toivonen L, Naukkarinen V *et al*. Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infarction. Eur Heart J 1999; 20: 111–20.
[6] Choy AM, Lang CC, Chomsky M *et al*. Normalization of acquired QT prolongation in humans by intravenous potassium. Circulation 1997; 96: 2149–2154.

[7] Chipperfield B, Chipperfield JR. Heart muscle magnesium and zinc concentrations after sudden death from heart disease. Lancet 1973; ii: 293–296.
[8] Haigney MCP, Shakoui W, Kaab S *et al*. Loss of cardiac magnesium in experimental heart failure prolongs and destabilizes repolarization in dogs. J Am Coll Cardiol 1998; 31: 701–706.
[9] Redwood SR, Taggart PI, Sutton PM *et al*. Effect of magnesium on the monophasic action potential during early ischemia in the in vivo human heart. J Am Coll Cardiol 1996; 28: 1765–9.
[10] Endoh I, Kasanuki H, Ohnishi S, Shibata N, Hosoda S. Influence of early coronary reperfusion on QT interval dispersion after acute myocardial infarction. PACE 1997; 20: 1646–53.

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Cardiogenic shock: a failure in reperfusion. Time for a strategic change?

See page 128 for the article to which this Editorial refers

Cardiogenic shock secondary to acute myocardial infarction results in the death of most affected individuals. This grim reality persists in spite of vigorous attempts at providing inotropic support using pharmacological agents, thrombolytic regimes and intra-aortic balloon pumping[1]. Reports of longitudinal data suggest that in spite of modern thrombolytic regimes, survival from cardiogenic shock is no better now than it was in the period 1975–1988[2]. These poor results may be attributed to patient presentation delay, treatment delay and decreased thrombolytic efficacy secondary to low perfusion pressure[3]. The most appropriate management strategy for individuals presenting with cardiogenic shock secondary to myocardial infarction therefore is controversial.

The acute and long-term survival of patients with myocardial infarction is most consistently associated with the patency of the infarct-related artery. Failure to achieve patency with thrombolytic agents is clearly associated with increased morbidity and mortality[4]. To avoid this deleterious outcome clinicians have employed more aggressive therapeutic strategies including intra-aortic balloon pumping with early revascularization. Recent studies including Hasdai's subgroup analysis from GUSTO III have suggested that early revascularization procedures in individuals with cardiogenic shock secondary to a failure in reperfusion after acute myocardial infarction may result in decreased mortality[5].

This leads one to consider an alternative, more aggressive strategy to achieve early infarct-related artery patency in all those presenting with acute myocardial infarction. All patients would be transported not to an emergency department but to a dedicated myocardial infarction centre (MIC) (Fig. 1). These units would be manned by interventional cardiologists, whose specific role would be to recognise those patients at increased risk from the sequelae of myocardial infarction and to re-establish infarct-related artery flow expeditiously. Thereby not only clinical parameters (haemodynamic stability, electrocardiogram and rhythm) but also angiography may be employed to stratify individuals at increased risk. This would enable immediate angioplasty and stent implantation of culprit lesions to be undertaken, allowing rapid, complete and sustained restoration of flow in the infarct-related artery. These patients may then be discharged from the myocardial infarction centre immediately to either a coronary care unit in the case of those requiring intensive monitoring and ongoing supportive treatment, or to low dependency wards in those with low pre-intervention risk. In those in the latter category, discharge home could

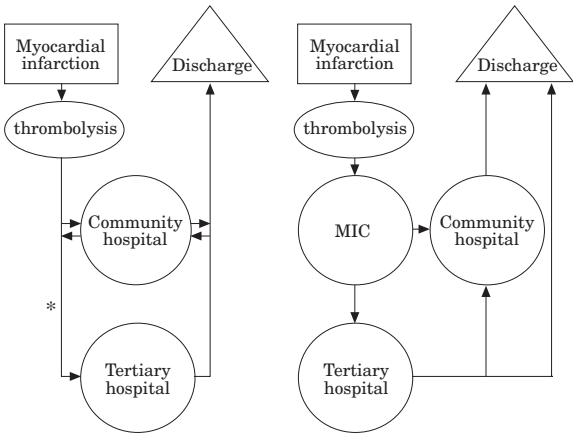

Figure 1 **Conventional model for the treatment of acute myocardial infarction. MIC=myocardial infarction centre; *failure of reperfusion or complications.**

occur within 3 days of the index myocardial infarction.

This strategy in no way precludes prior thrombolysis. Recent evidence suggests that rescue PTCA after failed thrombolysis is not associated with increased catheterization laboratory or procedural rates of complication[6]. Community thrombolysis and subsequent patient hospital transfer has proven to be safe[7], as has transfer of patients from community hospitals to tertiary centres after failed reperfusion[8]. It may be reasonable to assume that immediate transfer of patients post angioplasty to a coronary care unit within the myocardial infarction centre or associated to a tertiary or community hospital will be at low risk to the patient.

The establishment of the myocardial infarction centre would clearly require considerable manpower and funding. However, it may decrease costs by identifying individuals at increased risk, and allowing their rapid definitive treatment, decreasing both morbidity and mortality. Amongst those at lower risk, rapid treatment would allow immediate step-down to less monitored, less expensive hospital beds and early discharge. These issues need to be confronted in an era of limited resources; however, they are no more difficult than those already overcome by our predecessors who established the coronary care unit in the 1960s[9].

The paper of Hasdai *et al*.[10] and those that have preceded them have heightened our awareness of cardiogenic shock secondary to myocardial infarction and enabled us to identify those individuals at increased risk. What we have failed to do, however, is to implement a programme which consistently improves the outcome of this group. Whilst we have made considerable progress in the treatment of acute myocardial infarction since the introduction of the coronary care unit in the 1960s, the change of the millennium may see a more invasive means of obtaining early patency in the infarct-related artery.

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References

[1] Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343: 311–22.
[2] Goldberg RJ, Gore JM, Alpert JS *et al*. Cardiogenic shock after myocardial infarction-incidence and mortality from a community wide perspective 1975–1988. N Engl J Med 1991; 325: 1117–22.
[3] Newby KL, Rutsch WR, Califf RM *et al*. for the GUSTO-1 Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996; 27: 1646–55.
[4] Simes RJ, Topol EJ, Holmes DR *et al*. for the GUSTO-1 Investigators. Link between the angiographic substudy and mortality outcomes in a large randomised trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. Circulation 1995; 91: 1923–8.
[5] Berger PB, Holmes DR, Stebbins AL *et al*. for the GUSTO-1 Investigators. Impact of an aggressive invasive catheterisation and revascularisation strategy on mortality in patients with cardiogenic shock in the global utilisation of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO-1) trial. Circulation 1997; 96: 122–7.
[6] Ross MR, Lundergan CF, Rohrbeck SC *et al*. for the GUSTO-1 Investigators. Rescue angioplasty after failed thrombolysis: Technical and clinical outcomes in a large thrombolysis trial. J Am Coll Cardiol 1998; 31: 1511–17.
[7] Grijseels EW, Bouten MJ, Lenderink T *et al*. Pre-hospital thrombolytic therapy with either alteplase or streptokinase. Practical applications, complications and long-term results in 529 patients. Eur Heart J 1995; 12: 1833–8.
[8] Zijlstra F, Arnoud WJ, Liem AL *et al*. Transferring patients for primary angioplasty. A retrospective analysis of 104 selected high-risk patients with acute myocardial infarction. Heart 1997; 78: 333–6.
[9] Lown B, Selzer A. Controversies in Cardiology: The coronary care unit. Am J Cardiol 1968; 22: 597–602.
[10] Hasdai D, Holmes Jr DR, Topol EJ *et al*. Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase. Results from GUSTO-III. Eur Heart J 1999; 20: 128–35.

European Heart Journal (1999) **20,** 89–92

Antibiotics for acute coronary syndromes: are we ready for megatrials?

See page 121 for the article to which this Editorial refers

The final report of the ROXIS study[1] shows that in patients with acute non-Q-wave coronary syndromes the beneficial effects of roxithromicyn on the combined end-points of death, myocardial infarction and severe recurrent ischaemia, observed at 30 days[2], were no longer statistically significant at 6 months.

Persistent benefit at 1 year was previously reported in stable, post-myocardial infarction patients, all seropositive for chlamydia and all treated in a one or two 3-day cycle with azithromycin, another macrolide antibiotic, which, at variance with the ROXIS study was associated with a significant reduction of anti-chlamydia antibodies[3]. At least some of the discrepancies between these two studies are related to differences in inclusion criteria (as only 50% were seropositive for chlamydia in the ROXIS study). However, irrespective of the discrepancies, the possibility of improving the average prognosis of acute coronary syndromes with antibiotic treatment is intriguing and raises two questions: (1) What are the actual mechanisms of the preventive effect of macrolide antibiotics? (2) Does the benefit apply to all patients with acute coronary syndromes?

In seeking answers to these fundamental questions it is useful to consider three issues.

The causes of occlusive coronary thrombosis

In acute coronary syndromes, thrombosis has become the fundamental target for therapy and prevention. Understanding why coronary thrombosis, instead of remaining a self-limiting step in vascular repair becomes a mechanism of disease, would open the way to additional novel forms of treatments. In principle, thrombosis can develop in response to two types of thrombogenic stimuli: a fissure of an atherosclerotic plaque as a result of purely mechanical forces (in this case, the size of thrombus is determined by the thrombogeneticity of the fissure); an inflammatory activation of the vessel wall (in this case the growth of the thrombus is proportional to the intensity and duration of inflammation).

These two causes are not mutually exclusive and, in both cases, the final acute occlusion of the vessel is also determined by the haemostatic and by the local vasoconstrictor response[4]. Inflammatory cytokines can cause a persistent, waxing and waning activation of the endothelium, abolishing its antithrombotic and vasodilator properties. They can also directly promote thrombosis, vasoconstriction and activation of metallo proteases which, digesting the intercellular matrix, increase vascular permeability, cause detachment of endothelial cells and lysis of the cap of vulnerable plaques at their thinnest site[5].

Only a minority of acute coronary thrombi are composed of red cells and fibrin (indicative of their development in the presence of blood flow stasis or as a result of intense thrombogenic stimuli). The majority of thrombi are largely composed of platelets, (which implies their gradual formation in flowing blood in response to weak, but persistent thrombogenic stimuli). In acute coronary syndromes such thrombi are often multiple and sometimes multilayered, suggesting a multiplicity and recurrence of thrombogenic stimuli. For recurring and for multiple platelet thrombi, a diffuse and recurring inflammatory reaction would represent a more plausible thrombogenic stimulus than a purely mechanical injury, and it would also more easily explain the common fluctuations in instability over a period of days and weeks[4].

Evidence of inflammation

Several histological studies have shown that inflammatory cells infiltrate underneath acute coronary thrombi with or without an associated plaque fissure. However, as coronary plaques with inflammatory cell infiltrates are also found in stable patients[6], they are insufficient on their own to explain the development of the instability. Thus inflammation, under some conditions, may contribute to the development of atherosclerosis; in other circumstances it may cause acute activation of the vascular wall with consequent local thrombosis and vasoconstriction (with or without plaque fissure)[4]. The pathogenetic role of inflammation is supported by the independent prognostic value of inflammatory markers such as C-reactive protein[7,8]. However, only about 50–70% of patients with Braunwald class III B unstable angina have elevated values of C-reactive protein[7,8]. In about 40–50% of these patients the elevation of C-reactive protein and of IL-6 persists at discharge and at 3 months and is associated with recurrent instability and myocardial infarction at 1 year follow-up[9]. The percentage of patients with elevated C-reactive protein on admission increases to 90% in patients in whom myocardial infarction was preceded by unstable angina, but decreases to 30% in patients in whom myocardial infarction was totally unheralded[10]. Thus an acute inflammatory reaction, detectable systemically, appears to be an independent determinant of prognosis in some patients with acute ischaemic syndromes, but is not detectable in all.

Such an inflammatory component may be the final common result of a variety of inflammatory stimuli, infectious and non-infectious and also of the individual immunological[11] and inflammatory[12] response.

Chronic infections and inflammatory markers

Undoubtedly chronic infections and their reactivation are plausible inflammatory stimuli. They may be associated with the development of atherosclerosis and/or with the precipitation of acute coronary syndromes[13–15]. Our group also found that seropositivity for *Helicobacter pylori* and cytomegalovirus was significantly higher in patients with atherosclerotic clinical syndromes than in controls, but we found no difference between patients with acute and chronic syndromes[16]. In the specific seropositivity for the helicobacter CAG A+[17] strain we failed to find differences between patients with chronic and acute coronary syndromes. We also failed to find evidence for replicating cytomegalovirus in coronary endoarterectomy specimens of unstable patients[18]. *Chlamydia pneumoniae* appears the most plausible infectious agent associated with the development of atherosclerosis[19], but there is no evidence of its association with the precipitation of acute coronary syndromes. In patients with severe unstable angina at the time of hospital discharge, we found that seropositivity for *C. pneumoniae* was present in only 60% of patients, a percentage similar to that found by Gurfinkel *et al*.[2] and it was less strongly correlated with 1 year prognosis than C-reactive protein levels[9].

Thus, although seropositivity for infectious agents appears correlated to a variable extent with atherosclerotic manifestations, some patients with atherosclerotic manifestations and with acute coronary syndromes are seronegative, many seropositive individuals have non-cardiac diseases and many apparently healthy controls are seropositive. Thus, there is a need for research into the determinants of organ targetting of inflammation and the immune and inflammatory response to possible infectious and non-infectious triggers.

Conclusions

The available data suggest that macrolide antibiotics have a beneficial effect, but the evidence is not conclusive. It is also unknown whether this putative beneficial effect is due to their effect on chlamydia, on other known or unknown infection agents or on inflammatory cytokines[20]. The benefits observed by Gupta *et al*.[3] could be related to an anti-infectious effect as they persisted long term. Those of Gurfinkel *et al*.[2] could be related to an anticytokine effect, as they were observed in unstable patients only up to 30 days. Gurfinkel *et al*.[1] estimate that 'close to 4000 patients should have been enrolled in order to achieve an 80% statistical power and that several clinical studies, in various stages of development will help determine if infection plays an important role'. Undoubtedly this approach could provide conclusive evidence that, on average, patients with acute coronary syndromes benefit from macrolide antibiotics.

However, mega-trials with very broad inclusion criteria, although attractive to both clinical investigators and medical industry, do not consider the possibility that only some of the patients included in the trial may benefit from the treatment and that they may benefit through different mechanisms[21,22].

In the complex pathogenetic scenario outlined above, there is no ground for generalizations. It appears unlikely that inflammation is an important pathogenetic component for all myocardial infarction patients, that inflammation only results from chlamidya infection and that the inflammatory response is similar in all patients with acute ischaemic syndromes. The indiscriminate treatment of acute coronary syndromes with a single magic bullet appears like a shot in the dark. Its success will depend on the prevalence in the treated group of patients in whom at least one of the key pathogenetic components is corrected by the therapy: the higher their prevalence in the treated groups, the more easily detectable the average beneficial effect. Using a non-cardiological example, it would be like treating an unselected group of anaemic patients with vitamin B12 or with iron or with folic acid supplements: the success of the different trials will depend on the prevalence of patients in whom anaemia is actually corrected by the treatment tested.

Mega-trial-based evidence that post myocardial infarction patients benefit from beta-blockers, aspirin, statins and ACE inhibitors already exist. Antibiotics might join this list. However, as the list of drugs shown to be beneficial in post-myocardial infarction patients becomes longer and longer, we should begin to investigate who benefits from what. We cannot continue to concentrate on improving some of the patients treated without considering the burden of multiple drug combinations on all the others and the exponentially growing health care costs.

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References

[1] Gurfinkel E, Bozovich G, Beck E *et al*. Treatment with the antibotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final report of the ROXIS study. Eur Heart J 1999; 20: 121–7.

[2] Gurfinkel E, Bozovich G, Daroca A *et al*. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. Lancet 1997; 350: 404–7.
[3] Gupta S, Leatham EW, Carrington D *et al*. Elevated chlamydia pneumoniae antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. Circulation 1997; 96: 404–7.
[4] Maseri A. Ischemic Heart Disease. A rational basis for clinical practise and clinical research. New York: Churchill Livingstone, 1995. 237–301.
[5] Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995; 91: 2844–50.
[6] van der Wal AC, Becker AE, Koch KT *et al.* Clinically stable angina pectoris is not necessarily associated with histologically stable atherosclerotic plaques. Heart 1996; 76: 312–16.
[7] Liuzzo G, Biasucci LM, Gallimore JR *et al*. Prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med 1994; 331: 417–24.
[8] Rebuzzi AG, Quaranta G, Liuzzo G *et al*. Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina. Am J Cardiol 1998; 82: 715–9.
[9] Biasucci LM, Liuzzo G, Caligiuri P *et al*. Elevated levels of C-reactive protein at discharge predicts recurrent instability in patients with unstable angina. Circulation In press.
[10] Liuzzo G, Biasucci LM, Caligiuri G *et al.* Preinfarction unstable angina is associated with an enhanced acute phase response to myocardial cell necrosis. Circulation In press.
[11] Caligiuri G, Liuzzo G, Biasucci LM *et al*. Immune system activation follows inflammation in unstable angina: pathogenetic implications. J Am Coll Cardiol 1998; 32: 1295–1304.
[12] Liuzzo G, Biasucci LM, Gallimore JR *et al*. Enhanced inflammatory response to coronary angioplasty in patients with unstable angina. Circulation 1998; 98: in press.
[13] Danesh J, Collin R, Peto R *et al*. Chronic infections and coronary heart disease: is there a link? Lancet 1997; 350: 430–6.
[14] Ellis EW. Infection and coronary heart disease. J Med Microbiol 1997; 46: 535–9.
[15] Gura T. Infections: a cause of artery-clogging plaques? Science 1998; 281 (5373): 35.
[16] Liuzzo G, Caligiuri P, Grillo RL *et al*. Helicobacter pylori and cytomegalovirus infections are strongly associated with the atherosclerosis, but are not responsible for instability of angina. (Abstr). J Am Coll Cardiol 1997; 29: S2-217A.
[17] Pasceri V, Cammarota G, Patti S *et al* Association of virulent Helicobacter Pylori strains with ischemic heart disease. Circulation 1998; 97: 1675–9.
[18] Kol A, Sperti G, Shani J *et al*. Cytomegalovirus replication is not a cause of instability in unstable angina. Circulation 1995; 91: 1910–13.
[19] Shor A, Kuo CC, Patton DL *et al*. Detection of Chlamydia Pneumoniae in coronary arterial fatty streaks and atheromatous plaques. S Afr Med J 1992; 82: 158–61.
[20] Martin D *et al*. Alternative hypothesis for efficacy of macrolides in acute coronary syndromes. Lancet 1998; 351: 1858–9.
[21] Maseri A, Cianflone D, Pasceri V *et al*. The risk and cost-effective individual patient management: the challenge of a new generation of clinical trials. Cardiovasc Drugs Ther 1996; 10: 751–8.
[22] Maseri A. Evidence based medicine: a progress but not a final solution. Clin Cardiol 1998; 21: 463–4.