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Beneficial Effects of the Opiate Antagonist Naloxone on Hemodynamics and Ventricular Function Following Coronary Artery Occlusion and Reperfusion in the Dog

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ABSTRACT

It has been shown that endogenous opioid peptides (EOP) subserve important roles in cardiovascular regulation and are involved in the pathophysiology of myocardial ischemia, contributing to the deleterious effects. The aim of this study was to evaluate the effects of the opiate antagonist naloxone on the hemodynamics and ventricular function following coronary artery occlusion and reperfusion in the dog, utilizing the technique of cardiac catheterization. During myocardial ischemia and reperfusion, it was found that in the control group, there was reduction in the aortic, left ventricular, right atrial, pulmonary arterial and wedge pressures, and in the left ventricular dP/dt. The reduction in the aortic, left ventricular and pulmonary arterial pressures, and left ventricular dP/dt were significantly attenuated by pretreatment with naloxone. The results indicate a regulatory role of EOP in the cardiovascular function and suggest a possible involvement of EOP in myocardial ischemia and reperfusion causing detrimental effects such as arrhythmias, bradycardia, hypotension and, as shown in this study, impaired hemodynamics and ventricular function. The beneficial effects of naloxone on circulatory dynamics may have clinical implications in the prevention and treatment of ischemic heart disease.

Key words: endogenous opioid peptide; opiate antagonist; naloxone; hemodynamics; ventricular function; myocardial ischemia and reperfusion.

I. Introduction

The endogenous opioid system includes three major families of peptides; dynorphin (derived from pre-proenkephalin B), endorphins (derived from pre-proopiomelanocortin) and enkephalins (derived from pre-proenkephalin A). Multiple forms of opioid peptides are derived from these major precursors and many of them possess potent cardiovascular properties.

Endogenous opioid peptides (EOP) and opioid receptors are widely distributed throughout the body (Hughes *et al.*, 1977). Since the identification of EOP and opioid receptors in the heart (Krumins *et al.*, 1985), it has become clear that EOP subserve important roles in cardiovascular regulation and are especially involved in various cardiovascular stress situations such as shock (Holaday, 1983), heart failure (Liang *et al.*, 1987) and myocardial ischemia (Fagbemi *et al.*, 1982), contributing to the respective deleterious effects. In an isolated heart preparation, it has been shown that morphine decreases the myocardial contractility and heart rate (Clo *et al.*, 1985). Beta-endorphin, likewise, has been demonstrated as causing cardiac arrhythmias and decreasing myocardial contractility (Lee *et al.*, 1984). In an *in vivo* preparation, administration of morphine, B-endorphin or dynorphin

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in the group receiving naloxone were 98 ± 9 mmHg, 115 ± 13 beats.minute^{-1} and 2506 ± 213 mmHg.s^{-1}, respectively.

Fig. 1 shows the effects of naloxone on the changes in arterial blood pressure and heart rate following coronary artery occlusion and reperfusion. Myocardial ischemia invariably caused a marked decrease in both blood pressure and heart rate. Pretreatment of naloxone before coronary artery occlusion and reperfusion significantly reversed the reduction in both blood pressure and heart rate.

Results of the investigations on hemodynamics and ventricular function are illustrated in Fig. 2. In the control group, there were pronounced reductions in Ao(syst), Ao(diast), LV(syst), LV(diast), RA, PA and PW pressures following coronary artery occlusion and reperfusion. LV dP/dt was also significantly diminished.

In marked contrast to the control, the reduction in the aortic, left ventricular and PA pressures, and LV dP/dt were significantly reversed after pretreatment with naloxone, followed by coronary artery oc-

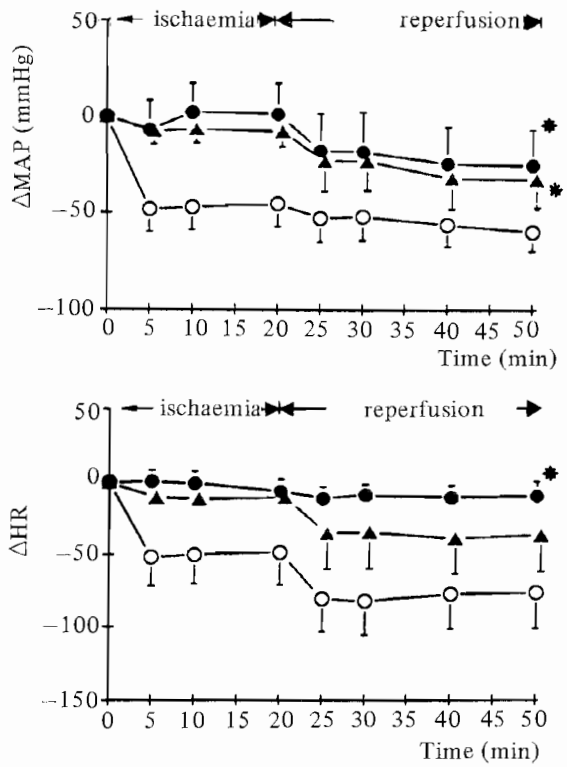
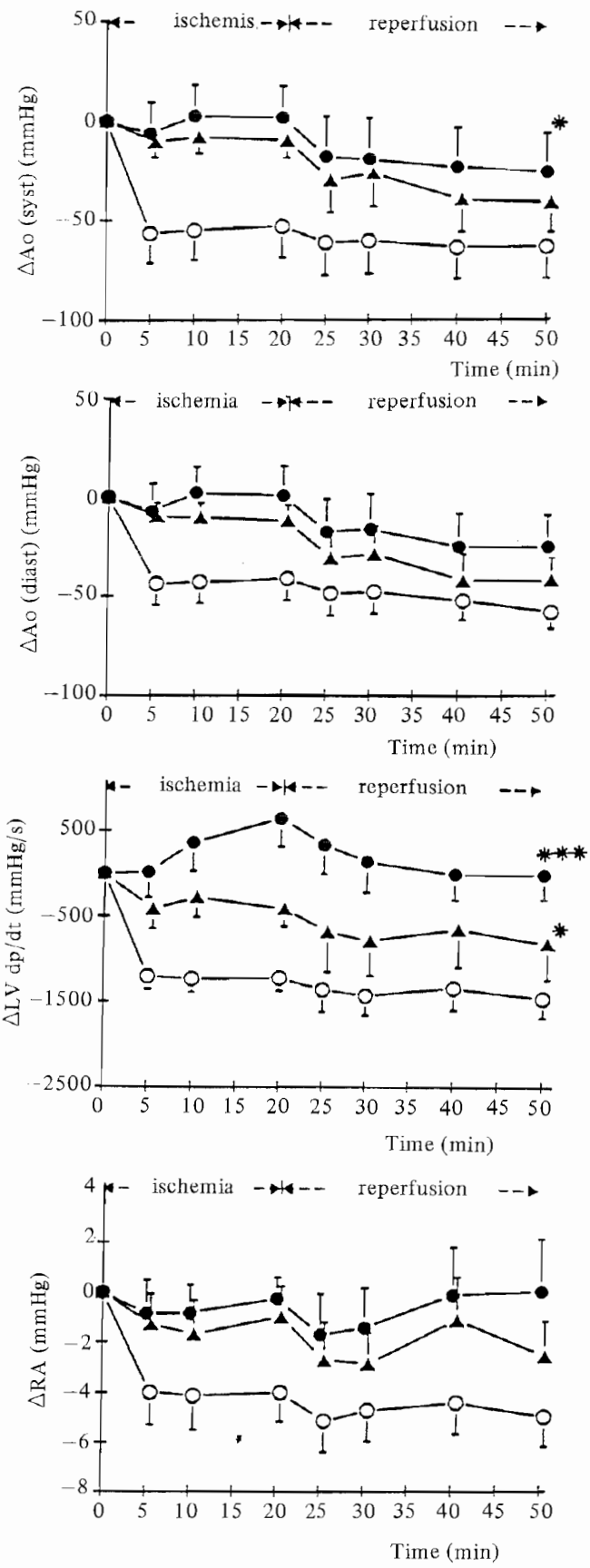


Fig. 1. Effects of naloxone on the changes in mean arterial pressure (△ MAP) and heart rate (△ HR) following coronary artery occlusion and reperfusion. (○) control; (▲) naloxone 0.92 μmole/Kg; (●) naloxone 2.75 umole/Kg. Values represent the means ± SEM of eight animals. *p < 0.05 vs control by analysis of variance.



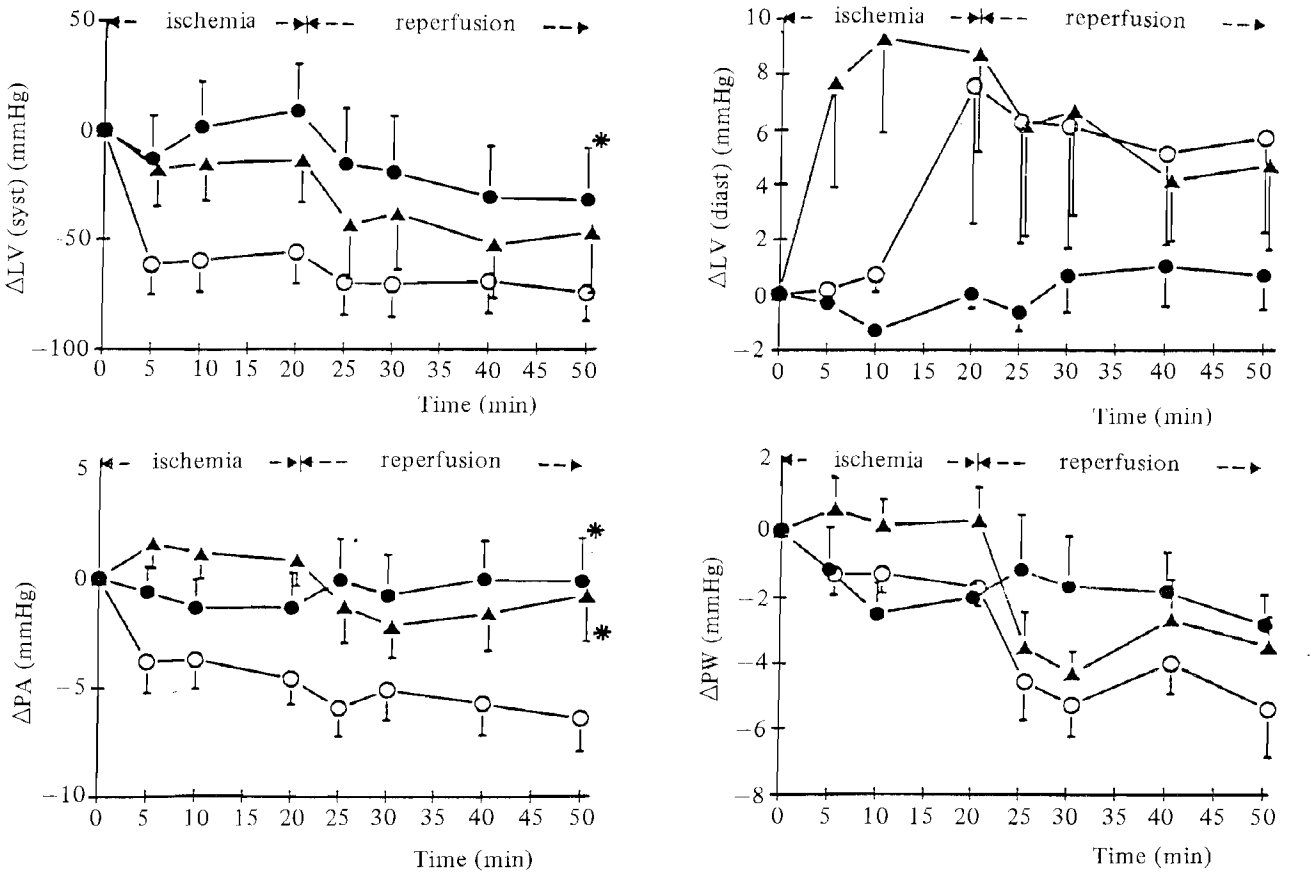


Fig. 2. Effects of naloxone on the changes in hemodynamics and ventricular function following coronary artery occlusion and reperfusion. (○) control; (▲) naloxone 0.92 μmole/Kg; (●) naloxone 2.75 μmole/Kg. Ao (syst) = systolic aortic pressure; Ao (diast) = diastolic aortic pressure; LV (syst) = systolic left ventricular pressure; LV (diast) = end-diastolic left ventricular pressure; LV dP/dt = first derivative of left ventricular pressure; RA = right atrial pressure; PA = mean pulmonary arterial pressure; PW = pulmonary wedge pressure. Values represent the means ± SEM of eight animals. *$p < 0.05$, ***$p < 0.001$ vs control by analysis of variance.

clusion and reperfusion. These cardiovascular effects of naloxone appeared to be dose-related. A lower dose of naloxone also reversed the reductions in aortic, left ventricular and PA pressures, and LV dP/dt following coronary artery occlusion and reperfusion, but to a lesser extent as compared with the higher dose of naloxone.

IV. Discussion

It is known that EOP may be released during various cardiovascular stress situations such as shock (Holaday, 1983), heart failure (Liang *et al.*, 1987) and myocardial ischemia (Fagbemi *et al.*, 1982), perhaps contributing to the respective cardiovascular dysfunction. Coronary artery occlusion and/or reperfusion has been demonstrated as leading to cardiogenic shock, bradycardia and arrhythmias, all of which are fatal complications secondary to acute myocardial infarction (Lee *et al.*, 1992). Similar effects were shown in the present study of the dog, in which coronary artery occlusion and subsequent reperfusion led to pronounced reduction in heart rate, arterial blood pressure, aortic, left ventricular, RA, PA and PW pressures, and LV dP/dt.

We have demonstrated an improvement in hemodynamics and ventricular function, characterized by a reversal of the above deleterious effects, in anesthetized dogs subjected to coronary artery occlusion and reperfusion. This observation is compatible with the previous findings that administration of naloxone improved survival in various forms of shock via a mechanism which resulted in an increase in blood pressure, cardiac output, stroke volume and cardiac contractility (Holaday, 1983). In the present study, pretreatment of naloxone restored the heart rate, arterial blood pressure, aortic and left ventricular pressures, probably by blocking and attenuating the

bradycardia and the depressor effects of EOP, which are believed to be released as a consequence of myocardial ischemia and reperfusion. The ischemia induced hypotension and bradycardia may also have been due to Bezold-Jarisch reflex, which is well-documented as a transient inhibitory reflex characterized by bradycardia with hypotension induced by stimulation of receptors situated in the left ventricle following coronary occlusion and reperfusion (Thoren, 1976). However, this cardiovascular reflex has been shown to be associated (Koren *et al.*, 1986) or not associated (Esente *et al.*, 1983) with myocardial salvage; whether it is a "cause" or "effect" of myocardial salvage is undetermined. Therefore, the relationship between the opioid system and the Bezold-Jarisch reflex in the modulation of blood pressure and heart rate remains to be elucidated. The elevation in PA pressure after treatment with naloxone may have been caused by an increase in venous return. The increase in LV dP/dt may have been due to the tendency toward elevated cardiac output and Ao (syst) pressure, or because of a direct inotropic effect of naloxone.

The efficacy of the opiate antagonist naloxone as a modifier of physiological events has been used as a tool to infer EOP in various systems. From that perspective, the effects of naloxone in the present study strongly implicate EOP as a factor in the pathophysiology of myocardial ischemia and reperfusion. Our results are also consistent with the hypothesis that EOP may be released from the heart upon myocardial ischemia and reperfusion, thus causing arrhythmias, hypotension, bradycardia or, as shown in this study, impaired hemodynamics and ventricular function (Lee, 1990). Naloxone, by virtue of its antagonistic action against opiates, rectifies these fatal complications secondary to myocardial ischemia and reperfusion, thus suggesting an important role of EOP in ischemic heart disease.

So far, investigation on the beneficial effects of naloxone in cardiovascular function is only at the preliminary stage. A detailed evaluation of the effects of opioid antagonists on cardiovascular hemodynamics and ventricular function is as yet lacking but highly needed. Without such information, a critical evaluation of the use of naloxone in myocardial infarction would be incomplete. It is hoped that the results of the present study may assist future assessment of the therapeutic value of naloxone, which may be important in the prevention and treatment of ischemic heart disease.

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鴉片抗劑納洛酮對冠狀動脈缺血再灌流性心血管功能之影響

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摘　要

已有報導，內生性鴉片樣　在心血管系統及心肌缺血病生理機轉上扮演重要角色。本研究利用心導管術進一步探討鴉片對抗劑（納洛酮）在心肌缺血再灌流時對心臟血行力學及心室功能的影響。對照組狗隻在經過冠狀動脈結紮再灌流時，主動脈、左心室、右心房、肺動脈及肺楔壓力，及左心室收縮力（dp/dt）皆下降。納洛酮則能有意義地減少主動脈及左心室壓及左心室收縮力下降。研究結果指出內生性鴉片樣　具心血管調控作用，及在心肌缺血再灌流時導致不良之心臟血行力學及心室功能，而納洛酮對血行力學及心室功能之改善作用，是經由抑制鴉片受體之影響。所以鴉片抗劑可能對心肌缺血性心臟疾病具預防及治療價值。