Is Myocardial Infarct Size Limitation by Ischemic Preconditioning an "All or Nothing" Phenomenon?[a]

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INTRODUCTION

The protective effect of a brief coronary artery occlusion on the development of myocardial necrosis during a subsequent longer lasting occlusion has only a limited duration ("ischemic preconditioning").[1,2] It has not been established, however, how the magnitude of this protective effect changes with time during the reperfusion period following the preconditioning stimulus. Because this knowledge may help elucidating the mechanism underlying ischemic preconditioning, we varied the duration of the reperfusion period following the preconditioning stimulus. Experiments were performed in pigs, a species in which the infarct size–limiting effect of ischemic preconditioning has been demonstrated[3,4] and in which functional coronary collaterals are absent so that interpretation of the results will not be complicated by a variable residual myocardial blood flow after a coronary artery has been occluded.

MATERIALS AND METHODS

Fasted, open-chest, pentobarbital-anesthetized pigs (28–32 kg) were randomly assigned to different experimental groups and instrumented as described earlier.[5] The

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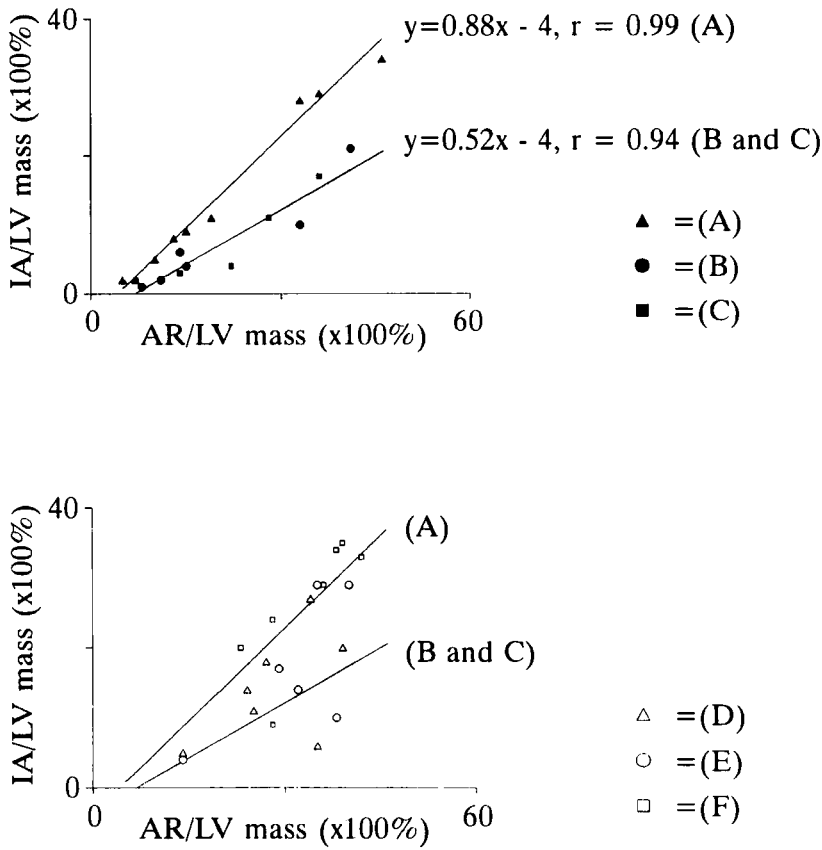

FIGURE 1. Top: The relationships between the infarcted area (IA) and the area at risk (AR), both presented as percentage of the left ventricular mass, of the control animals (Group A), which had a 60-min coronary artery occlusion (CAO), and the preconditioned animals of Groups B and C, which had a preceding 10-min CAO followed by 15-min and 60-min reperfusion, respectively, have been depicted. **Bottom:** The regression lines for Group A and Groups B and C are shown, together with the individual data of the animals, which had a preconditioning stimulus followed by 120-min (D), 180-min (E), or 240-min (F) reperfusion.

control group (A) involved a 60-min coronary artery occlusion (CAO) followed by 120 min of reperfusion. In all other animals the 60-min CAO was preceded by a single 10-min CAO. In these animals the reperfusion period (R) between the 10-min and the 60-min CAOs was 15 min (B), 60 min (C), 120 min (D), 180 min (E), or 240 min (F). In each group the area at risk (AR) of the individual animals was varied by occluding the left anterior descending coronary artery or its branches at different sites. During the experimental protocol, continuous recordings were made of the ECG, systemic hemodynamic variables and systolic segment length shortening (SS), while needle biopsies for determination of ATP, ADP, creatine, creatine phosphate, and energy charge were collected at intervals. At the end of the experimental protocol AR was identified and the infarcted area (IA) was determined.[6]

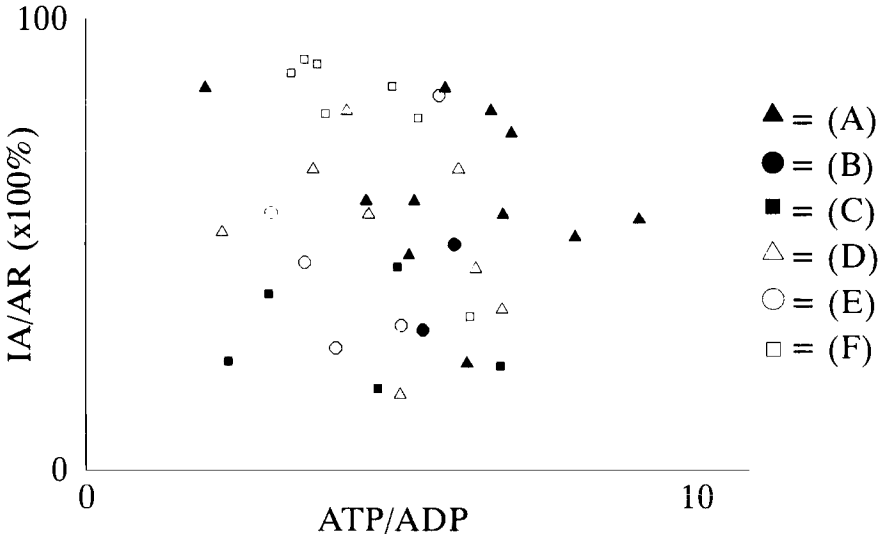

FIGURE 2. The relation between the infarcted area (IA) as percentage of the area at risk (AR) and ATP/ADP before the 60-min coronary artery occlusion (CAO). Data are from the control animals (A; 60-min CAO) and the animals in which the 60-min CAO was preceded by a 10-min CAO preconditioning stimulus followed by reperfusion periods of 15 min (B), 60 min (C), 120 min (D), 180 min (E) or 240 min (F).

RESULTS AND DISCUSSION

In the control Group A, SS decreased from 16 ± 1% to 2 ± 1% during the 60-min CAO. This loss in function was independent of AR. During the subsequent 120-min R there was no recovery of function (3 ± 1%). In these animals, IA was linearly related to AR (FIG. 1). In the other groups, the 10-min CAO also resulted in a loss of SS (from 19 ± 2% to 4 ± 2%) and a partial recovery (to 12 ± 1%) independent of the duration of R. In Groups B and C, the slope of the line describing the relation between IA and AR was significantly reduced compared to the slope found for Group A, indicating infarct size limitation (FIG. 1). In Groups D and E, the protective effect of preconditioning was lost in several animals, while still conspicuously present in others (FIG. 1). Preconditioning was completely lost in all but one of the animals of Group F. IA/AR proved not to be related to any of the metabolic variables prior to 60-min CAO (or the change from baseline). In FIGURE 2 the lack of relation between ATP/ADP and IA/AR has been depicted.

Our working hypothesis was that the protective effect of preconditioning would decrease gradually as the duration of the reperfusion period between 10-min CAO and 60-min CAO was extended. Such an observation would be consistent with a decrease in the concentration of a substance (circulating or present in tissue) responsible for the infarct size limitation. Our data, however, did not reveal such a gradual decrease when the reperfusion period was extended to 120 min or longer. Our data may therefore point towards an "all or nothing" phenomenon, which suggest a different type of mechanism.

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