RESPIRATORY CHAIN \( O_2 \) REQUIREMENTS AND THE METABOLIC ANSWER TO DIFFUSE ISCHEMIA OF MECHANICALLY OVERLOADED LEFT VENTRICULAR MYOCARDIUM*

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INTRODUCTION

Cardiac adaptation to mechanical overload proceeds in a three step manner (Meerson, 1969). After a short transitional period, a new steady state is usually attained before the heart fails. This period of enhanced metabolic activity (compensatory cardiac hypertrophy) can sometimes last over several weeks. In rats with a surgically induced aorto-caval communication (Hatt et al., 1980a), the compensated cardiac hypertrophy can persist over several months. Morphologically, the hearts from rats with a prolonged volume overload exhibit a decreased vascularization of the left ventricle (Rakusan et al., 1980). At the cellular level, the persistence of an activation of protein synthesis was suggested (Hatt et al., 1980a), the size of the left ventricular myocytes are increasing (Hatt et al., 1980b) and quantitative changes in intracellular organization appear (Anversa et al., 1971). The most striking modification is the increase in numerical density of the mitochondria resulting in an improved surface/volume ratio of mitochondria and decreased oxygen requirements for mitochondrial function (decreased cytochrome oxidase apparent \( K_M[O_2] \); Moravec et al., 1981). In this work we tried to quantify the range of intracellular \( P_O_2 \)'s compatible with the unimpaired mitochondrial function (full oxidation of the cytochrome oxidase). The hemodynamic and metabolic effects of an acute ischemia (one-way valve, working heart preparation) were

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also tested in order to evaluate the resistance of the left ventricular myocardium to a decreased oxygen supply.

METHODS

An aorto-caval communication was surgically created in young female Wistar rats. Sham-operated animals were used as controls. Three experimental and two control rats were caged together. The animals were sacrificed 3 months after the surgery. The majority of these animals exhibited a compensatory heart hypertrophy. The animals having peripheral signs of congestive heart failure were rejected from further study. One group of hearts, half with a fistula and half without (total number 40) was atrially perfused with bicarbonate buffer containing 10 mmol·l⁻¹ glucose. In some cases 1.5 mmol·l⁻¹ palmitate was added to the glucose-containing solution (Feuvray et al., 1981). The perfusate (200 ml) was recirculated. All hearts were preperfused for 15 min. Then, in some of them, a 50% reduction of coronary flow was induced by the insertion of a one-way valve into the aortic outflow tract (Neely et al., 1973). Left ventricular function was assessed by monitoring the aortic pressure and the heart rate. The aortic flow was measured by means of a rotameter. At the end of the perfusion, the hearts were deeply frozen in liquid nitrogen and the ventricular fragments processed for ATP, CP, ADP, Pi determinations. An aliquot of frozen tissue was used for CoA and long chain acyl-CoA (Garland et al., 1965) determinations. Tissue carnitine and long chain carnitine were determined by a radio isotope procedure (Mc Garry and Foster, 1976). A separate group of hearts was used to assess the oxygen requirements of the mitochondrial function (Moravec et al., 1981). These hearts were perfused at 37°C and 70 Torr according to Langendorff (non-working heart preparation). Two parallel columns of the perfusion fluid containing 10 mmol·l⁻¹ glucose were equilibrated with either 95% O₂ and 5% CO₂ (Po₂ 620 Torr) or 95% N₂ and 5% CO₂ (40 Torr) and connected to the aortic cannula by means of a miniature solenoid valve (General Valve Corporation) with negligible dead space. This allowed abrupt changes in the rate of oxygen delivery to the tissue. All hearts were pre-perfused for 10 min with the oxygenated solution, then they were subjected to several 2 min anoxic periods followed by reoxygenation (state 5-to-state 3 transition). During the reoxygenation phase, the cytochrome oxidase reduction and the myoglobin O₂ saturation were monitored by means of a rapid scanning spectroscope according to Lübbers and Niesel (1959). Care was taken to alternate the cytochrome aa₃ and myoglobin recordings and only those hearts whose individual responses were reproducible were considered. The superposition of successive cytochrome aa₃ and myoglobin double wavelengths recordings allowed an evaluation of the range of intracellular Po₂'s necessary to maintain the cytochrome oxidase full oxidation using the Theorell's equation for the myoglobin dissociation curve read at 37°C (Leniger-Pollert and Lübbers, 1973). In some