myocardium. In that study, however, we did not differ-
tentiate between the basal VO₂ and the MVO₂ for excitation-
contraction coupling. To assess whether the basal metabolism is disturbed in the stunned myocar-
dium, we performed experiments on isolated, blood-
perfused rabbit hearts, and hemodynamic variables and VO₂ were assessed during control, in postischemic, reperfused myocardium, and during subsequent cardiac arrest after KCl administration. For comparison, basal VO₂ was assessed in normal hearts both during control and after KCl administration.

**MATERIALS AND METHODS**

Experimental preparation. Experiments were performed on a total of 22 male New Zealand White rabbits with an average age of 6 mo and an average body mass of 3,500 ± 850 g; the rabbits were handled according to the animal welfare regulations of the German federal authorities. The hearts were reperfused, and VO₂ was measured 5 min after a 5 min KCl solution containing 4 g/100 ml albumin, and the concentration of free Ca²⁺ was adjusted to 2.5 mM. The recirculating erythrocyte suspension was oxygenated using a pediatric hollow fiber oxygenator (Masterflo 34, Dideco). The gas mixture contained 72% N₂-22% O₂-6% CO₂. The perfusate temperature was held at 38°C, and the coronary arterial pressure was measured using a servo-controlled roller pump (SOSL, Watson Marlow).

A water-filled latex balloon (no. 12-14, H. Sachs Elektronik) was inserted into the left ventricular (LV) cavity through the mitral valve. The balloon was connected to a "systemic" circuit that contained two artificial valves and a windkessel. An ultrasonic flow probe in connection with a flowmeter (T-206, Transonic Systems) was used to measure aortic flow, and a pressure transducer (P23 XL, Statham) was used to measure aortic pressure as an index of LV afterload. This circuit permitted independent changes in preload and afterload conditions. A 3-F microtip manometer (TC-500, Millar) was inserted into the balloon to measure LV pressure. For measurement of left intraventricular diameter, sonomicrometry was performed (System 6, Triton) with the use of piezoelectric crystals that were glued to either side of the balloon. Blood from the right heart was drained via a cannula placed in the pulmonary artery to measure total coronary blood flow (CBF) using another ultrasonic flow probe. The difference in arterio-
venous O₂ content (a-vO₂) was continuously measured using absorption spectrophotometry (AVOX systems; Ref. 29). This system was independently calibrated using measurements provided by a Lex-O₂-Con analyzer.

Experimental protocol. After the experimental instrumentation was completed and the ventricular function was stabilized, control measurements were made. In a nonischemic control series (n = 8), 5 ml KCl, corresponding to a final concentration of 20 mM, were injected into the arterial line to induce cardiac arrest. CBF and aVO₂ were measured 5 min after KCl arrest. In a second series (n = 14), the hearts were...
subjected to a period of 20 min of normothermic, no-flow ischemia. Thirty minutes after the onset of reperfusion, data were again recorded. The same KCl dose was then injected, and CBF and a-vO2 were measured 5 min thereafter. During control and reperfusion, coronary arterial pressure was held constant (80 ± 2 mmHg). All variables were assessed at a constant temperature of 38°C maintained by immersing the hearts in a temperature-controlled chamber filled with venous blood. LV preload, estimated using intraventricular diameter, was maintained constant as well. The hearts were weighed at the end of the protocol.

Data acquisition. The following variables were continuously recorded with an eight-channel, forced-ink chart recorder (type 481, Brush): aortic flow, LV pressure, first derivative of pressure over time (dP/dt), intraventricular diameter, CBF, and a-vO2. To exclude afterload-dependent changes, peak systolic pressure and maximum and minimum dP/dt (dP/dtmax and dP/dtmin) were recorded while the outflow tract was temporarily cross clamped. The data were simultaneously stored on magnetic disk after digitization at a sampling rate of 300 Hz for later analysis using a custom-made computer program (EASYDAT; Ref. 4).

Calculations and statistics. Hemodynamic data were analyzed via the same computer program (EASYDAT; Ref. 4). Heart rate, dP/dtmax, and dP/dtmin were derived from the LV pressure signal. CBF was normalized to 100 g wet wt. MV˙O2 was calculated according to the Fick principle from the normalized CBF and the a-vO2.

Data are presented as means ± SD. Statistical analysis was performed with an IBM-compatible personal computer and a statistical software package (SYSTAT; Ref. 37). All variables were compared with the use of one-way analysis of variance. A P value < 0.05 was considered indicative of a significant difference.

RESULTS

Control series. Control heart rate was 163 ± 30 beats/min, aortic flow was 39 ± 18 ml/min, maximum isovolumic LV pressure (LVPmax) was 112 ± 36 mmHg, and dP/dtmax was 1,260 ± 410 mmHg/s. Early LV relaxation, assessed using dP/dtmin, was −1,215 ± 520 mmHg/s. CBF was 99 ± 33 ml·min−1·100 g−1, and a-vO2 was 7.4 ± 1.6 ml/100 ml. Thus MV˙O2 was equal to 7.0 ± 1.8 ml·min−1·100 g−1.

After KCl arrest, CBF decreased to 19 ± 17 ml·min−1·100 g−1, whereas the a-vO2 increased to 9.6 ± 3.8 ml/100 ml. MV˙O2 was 1.2 ± 0.5 ml·min−1·100 g−1.

Postischemic reperfused hearts. During control, heart rate was 137 ± 23 beats/min, aortic flow was 40 ± 14 ml/min, isovolumic LVPmax was 120 ± 18 mmHg, and dP/dtmax was 1,175 ± 270 mmHg/s. Early relaxation, assessed using dP/dtmin, was −980 ± 255 mmHg/s. CBF was 78 ± 28 ml·min−1·100 g−1, and total MV˙O2 was 5.3 ± 1.1 ml·min−1·100 g−1.

Heart rate in the postischemic reperfused hearts was 126 ± 25 beats/min (not significant), and aortic flow was 4 ± 4 ml/min. LVPmax (66 ± 9 mmHg), dP/dtmax (545 ± 265 mmHg/s), and early relaxation (dP/dtmin, 440 ± 246 mmHg/s) were significantly impaired. In parallel with these functional changes, CBF decreased to 61 ± 27 ml·min−1·100 g−1, and MV˙O2 decreased to 3.4 ± 3.3 ml·min−1·100 g−1.

After subsequent KCl arrest, CBF decreased to 14 ± 5 ml·min−1·100 g−1, and MV˙O2 was 0.5 ± 0.3 ml·min−1·100 g−1.

In hearts from a previous series (28), the variables during control were comparable with the variables from the present study, and they were similarly changed at 30 min of reperfusion after 20 min of global ischemia. In that series, the linear relationship between the pressure-volume area (PVA) and the total MV˙O2, which provides both the contractile efficiency (inverse slope) and the MV˙O2 for the unloaded contraction (MV˙O2 axis intercept), was assessed. The contractile efficiency significantly decreased (31 ± 18 vs. 14 ± 7%), whereas MV˙O2 for the unloaded contraction did not (3.8 ± 1.3 vs. 3.4 ± 0.9 ml·min−1·100 g−1).

DISCUSSION

The main finding of the present study on isolated, blood-perfused rabbit hearts is that the basal metabolism is not elevated in stunned myocardium compared with that in nonischemic myocardium. Thus this fraction of MV˙O2 does not account for the inappropriately high Vo2 compared with the impaired systolic and diastolic contractile function.

Ventricular function. The decreased global measures in both our previous (28) and present studies on isolated hearts are in concert with results from in situ investigations that had already shown impaired systolic (9, 25, 33) and diastolic (7, 11, 36) function in the postischemic reperfused myocardium.

Total MV˙O2 in stunned myocardium. Possible causes that have been suggested for the contractile dysfunction persisting despite normal MV˙O2 include uncoupling between substrate metabolism and energy production, accelerated but useless energy drainage (19), or some impairment between energy transfer and the function of contractile proteins (6, 19). In addition, increased ATP requirements for force generation by the myofilaments were suggested to be responsible for inadequate MV˙O2 (5). In a previous study (28), stroke work was decreased by as much as 80%, whereas total MV˙O2 was decreased by only ~16%. Thus the ratio between stroke work and MV˙O2 (index of external efficiency) was drastically reduced in the postischemic reperfused myocardium, showing that the postischemic myocardium is energetically inefficient (1, 5, 16, 26).

Such conditions might become important clinically if function in the stunned myocardium is augmented after inotropes or during exercise, because the additionally supplied O2 during positive inotropic stimulation will only inefficiently be converted into energy, such that ischemia can likely be induced again.

MV˙O2 for the unloaded contraction. The MV˙O2 for the unloaded contraction was obtained via extrapolation of the linear relationship between total MV˙O2 and the PVA. This framework allows separate analysis of the MV˙O2 that is associated with ventricular work (PVA dependent) vs. excess MV˙O2 and MV˙O2 that is non-work related (MV˙O2 for the unloaded contraction; Ref. 32). In a previous study (28), it was shown that the MV˙O2 for the unloaded contraction was not decreased in the
stunned myocardium. Similar results were obtained in a study (23) on isolated, blood-perfused canine hearts. The MVO₂ for the unloaded contraction increases with increasing contractile state (32) and decreases with decreasing contractile state (31). With respect to the depressed contractile state in the stunned myocardium, this MVO₂ fraction was inappropriately high.

Contractile efficiency. The linear relationship between MV˙O₂ and the PVA describes the contractile efficiency (32), i.e., the relationship between the contraction and the O₂ needed for that contraction (30). Contractile efficiency for the stunned myocardium was clearly decreased in our previous study (28), suggesting an abnormality in the contractile process (16) or some impairment between energy transfer and function of contractile proteins (19). This result is in contrast, however, with the increased contractile efficiency reported from cross-circulated, isolated canine hearts (23), a finding that might be explained with different MV˙O₂ levels during control (4.5 ml·min⁻¹·100 g⁻¹ in canine hearts vs. 5.7 ml·min⁻¹·100 g⁻¹ in rabbit hearts) or that might be attributed to species-dependent differences.

MVO₂ in the arrested heart. The MVO₂ for the unloaded contraction includes one fraction for basal myocardial metabolism and another for excitation-contraction coupling. To determine which of the two fractions had changed, the basal MVO₂ was assessed in this study after cardiac arrest. Basal MVO₂ averaged 0.5 ± 0.3 ml·min⁻¹·100 g⁻¹, which is significantly lower than that in the nonischemic, arrested hearts (1.2 ± 0.5 ml·min⁻¹·100 g⁻¹). In cross-circulated, isolated canine hearts (23), the basal MVO₂ in postischemic hearts was also lower compared with that in control hearts. That this apparent difference was not statistically significant might be explained with the lower MVO₂ levels during control in that study (4.5 vs. 5.7 ml·min⁻¹·100 g⁻¹). On the other hand, we cannot exclude species-dependent differences.

Basal MVO₂ in nonischemic, arrested hearts from different species varies from ~2.0 to 3.5 ml·min⁻¹·100 g⁻¹ (17, 20, 22, 34, 35). In contrast, values can be as low as 1.0 ml·min⁻¹·100 g⁻¹ (12, 16, 21, 23, 35). So far, the lowest basal MVO₂ values reported from nonischemic hearts before arrest are equal to 0.6 (3) and 0.7 ml·min⁻¹·100 g⁻¹ (13). These three different levels suggest that it is difficult to define and measure basal MVO₂. Obviously, the values depend on several factors such as time of measurement after cardiac arrest, perfusion pressure, temperature, and type of arrest (20), conditions that were comparable for the three series reported in this study.

In summary, the basal MVO₂ in stunned hearts is lower compared with prestunning levels. Therefore, the relatively high MVO₂ in stunned myocardium cannot be explained by repair processes taking place during that condition (2, 8). This notion would be in concord with a previous study on isolated rabbit hearts that were buffer perfused (16) and with a study on excised, cross-circulated canine hearts that focused on the increased O₂ cost of contractility in the stunned myocardium (23).

The maintained MVO₂ for the unloaded contraction suggests that the fraction of MVO₂ attributable to excitation-contraction coupling is disproportionately high in stunned myocardium and, in fact, impairment of Ca²⁺ handling has frequently been held to be responsible (14–16, 24). The reduced contractile efficiency, in addition, is indicative of an impaired O₂ utilization by the contractile apparatus. We suggest that, besides the functional, vascular, and electrical stunning, a “metabolic stunning” exists.

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