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Temporal dynamics of inotropic, chronotropic and metabolic responses during ß$_1$- und ß$_2$-AR stimulation in the isolated, perfused rat heart

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Abstract:

Temporal dynamics of inotropic, chronotropic and metabolic responses during ß$_1$- and ß$_2$-AR stimulation in the isolated, perfused rat heart. During the ß-adrenergic receptor (ß-AR)-mediated stress response in the heart, the relations between functional responses and metabolism are ill defined, with the distinction between ß$_1$- and ß$_2$-AR subtypes creating further complexity. Specific outstanding questions include the temporal relation between inotropic and chronotropic responses and their metabolic correlates. We sought to elucidate the relative magnitudes and temporal dynamics of the response to ß$_1$- and ß$_2$-AR stimulation and the energy expenditure and bioenergetic state related to these responses in the isolated perfused rat heart. Inotropic [left ventricular developed pressure (LVDP) and d*P*/d*t*], chronotropic [heart rate (HR)], and metabolic responses were measured during ß$_1$- (n = 9; agonist: norepinephrine) and ß$_2$- (n = 9; agonist: zinterol) AR stimulation. Myocardial oxygen consumption (MVo_2) was measured using fiberoptic oximetry, and high-energy phosphate levels and intracellular pH were measured using ^{31}P NMR spectroscopy. A multiple-dose protocol was used, with near-maximal ß-AR stimulation at the highest doses. In both ß1 and ß2 groups, there were dose-dependent increases in LVDP, d*P*/d*t*, HR, and MVo_2. The inotropic response showed more rapid onset, washout, and variation during dose than did the chronotropic response and was closely correlated with MVo_2. This suggests that the myocardial bioenergetic state is more closely related to the inotropic response than to the chronotropic response. In addition, ß$_1$-AR stimulation resulted in a greater magnitude and rate of onset of inotropic and MVo_2 responses than did ß$_2$-AR stimulation during maximal stimulation. However, a similar decrease in intracellular energy charge was seen in the two groups, consistent with a greater rate of oxidative phosphorylation during ß$_1$- than during ß$_2$-AR stimulation.

Key-words: Receptors, adrenergic, metabolism, myocardial oxygen consumption, inotropy, chronotropy, phosphorus-31 nuclear magnetic resonance, rat heart, adrenergic receptor