

# Effects of Digoxin on Myocardial Oxygen Supply and Demand in Patients Following Coronary Artery Bypass Surgery

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Although digoxin is used frequently in patients in the prophylaxis of postoperative supraventricular tachyarrhythmias, the effects of the drug on myocardial oxygen supply and demand after coronary bypass have not been described. Seven adult patients with good ventricular function who underwent myocardial revascularization were studied before and three hours after digoxin (0.5 mg, iv). There were no significant changes observed in any measured systemic hemodynamic variable. Evaluation of global myocardial metabolism showed an increase in myocardial oxygen consumption ( $P < 0.05$ ) which was compensated satisfactorily, as no significant alteration was noted in the coronary sinus oxygen content, or in the lactate gradient across the myocardium.

Since the authors studied the effects of only one dose of digoxin, the effects of full digitalization in these patients remains to be defined. (Key words: Anesthesia; cardiovascular. Heart; blood flow, myocardial; coronary occlusion; digitalis; metabolism; oxygen consumption. Surgery; cardiovascular.)

DIGITALIS GLYCOSIDES have been used for decades in the management of patients following cardiac surgery.<sup>1-7</sup> The most frequent use of digoxin in patients after myocardial revascularization is in the prophylaxis and therapy of postoperative supraventricular tachyarrhythmias.<sup>8-11</sup> In addition, the drug may provide cardiac reserve to the postoperative patient in whom left ventricular dysfunction occurs without clinical heart failure. Any consideration of these benefits must be made in relation to the effects of the drug on myocardial oxygen supply and demand, since digoxin may impose an undesirable metabolic cost to the myocardium simultaneous with its clinical effect.<sup>12-15</sup> An evaluation of the metabolic cost of digitalis administered for arrhythmia prophylaxis following myocardial revascularization has not been described. Accordingly, the goal of the present study was to examine the acute effects of digoxin on myocardial

oxygen consumption and myocardial lactate extraction in conscious patients following coronary artery bypass surgery, relating the data to concurrent changes in hemodynamics.

## Materials and Methods

According to a protocol approved by the Human Subjects Committee of this institute, seven patients (6 male, 1 female; age,  $58 \pm 8$  years [mean  $\pm$  SD]) were studied. Informed consent was obtained from all patients. The study was done in the Cardiac Surgical Intensive Care Unit on the day following surgery. All patients were conscious and in the fasting state. The patients had not received a digitalis preparation for at least 72 h before the study. Two patients were on chronic beta-adrenergic blockade therapy; the last dose of propranolol was 36 h before the study. One patient required 4 mg morphine sulfate subcutaneously for incisional pain 2.5 h before the study. The other patients had received 2-4 mg morphine, iv, or subcutaneously 6-15 h before the study. Of the remaining patients, none received a vasoactive drug whose effect might persist at the time of study.

All patients had preoperative chronic stable angina or medically responsive unstable angina. Although 4/7 patients had previous documented myocardial infarctions, mean angiographic ejection fraction was normal ( $0.71 \pm 0.11$ ). Three patients had single-vessel disease, and two patients each had double- or triple-vessel disease of the coronary arteries. Each of the patients was judged to be completely revascularized by the surgeon (range of number of grafts inserted: 3-5), as all vessels with greater than 50 per cent obstruction were bypassed.

One patient developed an intraoperative myocardial infarction as assessed by the presence of serial electrocardiographic and serum enzymatic changes. The infarct was small and well-tolerated; at the time of study the patient had a cardiac index of  $3.27 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ . This patient's metabolic response to digoxin was not substantially different from the other patients who did not develop an intraoperative myocardial infarction.

The following catheters were introduced in each patient: (1) an 18-gauge cannula in the radial artery; (2) a thermodilution triple-lumen catheter (Edwards) by the Seldinger technique through the right internal jugular vein into the pulmonary artery; and (3) a coronary sinus catheter (Wilton-Webster Laboratories, Altadena, California) by the same route and technique into the coro-

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TABLE 1. Hemodynamic Response to Digoxin in Patients (N = 7) Following Coronary Artery Bypass Surgery

	Intervention	HR (beats/min)	MAP (mmHg)	PCW (mmHg)	SVR (dyne · s · cm <sup>-5</sup> )	CI (l · min <sup>-1</sup> · m <sup>-2</sup> )
Mean ± SD	Before After	85 ± 10 90 ± 9 NS	89 ± 10 87 ± 12 NS	10 ± 3 9 ± 2 NS	1,129 ± 241 1,066 ± 237 NS	3.17 ± 0.3 3.30 ± 0.3 NS

Abbreviations: HR = heart rate; MAP = systemic mean arterial pressure; PCW = mean pulmonary capillary wedge pressure; SVR

= systemic vascular resistance; CI = cardiac index; NS = not significant.

nary sinus by fluoroscopy, such that the external thermometer was 10–20 mm inside the coronary sinus.

After control measurements, digoxin (0.5 mg) was infused over a period of five minutes into an arm vein through the side-arm of an infusion tubing. The patient was unaware that the drug was being administered. Coronary sinus blood flow was measured by the thermodilution technique as described by Ganz *et al.*<sup>16</sup> Arterial and coronary sinus blood samples were obtained simultaneously for determination of lactate and oxygen concentrations. Lactate samples were analyzed in duplicate by a modification of the Marbach method.<sup>17</sup> Blood samples were analyzed immediately for O<sub>2</sub> saturation and hemoglobin concentration (IL CO-oximeter, model 282). Oxygen content (ml O<sub>2</sub>/dl) was calculated as: Hb × O<sub>2</sub> per cent saturation × 1.34. Systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were measured and recorded on paper using a 6-channel chart recorder (VR-6 Electronics for Medicine). Cardiac outputs were measured in duplicate by thermodilution. Arterial blood pressure, EKG lead II, and the patient's clinical condition were monitored continually. Measurements were repeated at 10, 30, and 180 min after the digoxin infusion.

Hemodynamic indices were calculated from pressure and output data according to standard formulae. Metabolic indices were calculated as follows:

$$\text{Lactate extraction ratio} = \frac{\text{ART (lactate)} - \text{CS (lactate)}}{\text{ART (lactate)}}$$

where ART (lactate) is the arterial lactate concentration (mEq/l) and CS (lactate) is the coronary sinus lactate concentration (mEq/l).

$$\text{MVO}_2 = \text{CBF} \times (\text{ART \{oxygen\}} - \text{CS \{oxygen\}})$$

where MVO<sub>2</sub> is oxygen consumption of the myocardium

drained by the coronary sinus (predominantly the left ventricular myocardium) and CBF is coronary blood flow.

Statistical evaluation was done using a Wilcoxon paired test comparing measurements before and after digoxin in each patient.

## Results

Hemodynamic data before and 180 min after the digoxin infusion for the group are shown in table 1. There were no significant alterations in any of the hemodynamic variables measured at any time after drug administration for the group as a whole. However, modest variation in hemodynamic function was noted in individual patients. Cardiac output slightly increased in two patients, but this was explained by increases in heart rate.

The myocardial metabolic results for the group are shown in table 2. Digoxin produced an increase in the calculated myocardial oxygen consumption in six patients, with a mean increase of 21 per cent for the entire group ( $P < 0.05$ ). This was accompanied by a parallel increase in coronary blood flow in four patients resulting in an overall nonsignificant 11 per cent increase for the group. The mean coronary sinus oxygen content for the group remained unchanged. Alterations in the mean global myocardial lactate extraction for the entire group were not significant.

The increase in myocardial oxygen consumption was not reflected by the rate-pressure product as an indirect index of this variable ( $r = 0.1$ ). None of the other measured or calculated hemodynamic variables correlated with the increase in myocardial oxygen consumption.

None of the patients experienced chest discomfort or adverse reactions during the study. Continued monitoring of EKG lead II revealed no alterations in cardiac rhythm, ST segments or T waves.

TABLE 2. Myocardial Metabolic Response to Digoxin in Patients (N = 7) Following Coronary Artery Bypass Surgery

	Intervention	CSBF (ml/min)	CVR (mmHg · ml <sup>-1</sup> · min)	CS-O <sub>2</sub> Content (ml/dl)	MVO <sub>2</sub> (ml/min)	MLE (Per Cent)	RPP
Mean ± SD	Before After	116 ± 35 129 ± 44 NS	0.73 ± 0.26 0.65 ± 0.24 NS	6.1 ± 0.5 6.2 ± 0.7 NS	7.2 ± 1.8 8.7 ± 2.1 $P = 0.046$	31 ± 17 20 ± 11 NS	12,366 ± 2,989 12,846 ± 3,003 NS

Abbreviations: CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; CS-O<sub>2</sub> = oxygen content in coronary sinus blood;

MVO<sub>2</sub> = myocardial oxygen consumption; MLE = myocardial lactate extraction; RPP = rate-pressure product.

## Discussion

Although digoxin is used frequently for arrhythmia prophylaxis following myocardial revascularization, the myocardial metabolic cost imposed by the drug in this setting is unknown. Our study examined the myocardial metabolic cost of digoxin, specifically its effects on myocardial oxygen supply and demand.

It is important to describe closely the patients studied, because results obtained in one clinical or hemodynamic setting may not apply to all patients. Each patient was judged to be completely revascularized by the surgeon. The study was performed the day following surgery, and each patient was hemodynamically stable with good ventricular function. The mean pulmonary capillary wedge pressure for the group was 10 mmHg, and the cardiac index was greater than  $2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , in each patient at the time of study. Thus, the patients did not have low output syndrome or congestive heart failure.

Hemodynamic studies on the acute cardiovascular effects of digoxin in the non-failing heart in the absence and presence of coronary artery disease<sup>14,15,18-20</sup> and in patients during and following myocardial infarction<sup>21,22</sup> have shown a consistent digitalis-related increase in myocardial contractility, with a decrease in left ventricular filling pressures. The cardiac output may not increase<sup>14</sup> or may even decrease.<sup>15</sup> In the present study, small variations were observed in the measured hemodynamic variables between patients, but no consistent change was noted. Although an increase in systemic vascular resistance has been described following a rapid infusion of digoxin,<sup>23</sup> this effect was not observed in our patients. Indeed, in most patients a slight fall in calculated systemic vascular resistance was observed.

Metabolic studies in non-operated patients with coronary artery disease and preserved ventricular function have shown that digitalis glycosides cause either no change or an increase in myocardial oxygen consumption as a result of an increase in myocardial contractility.<sup>14,15</sup> In these studies, the increased oxygen demand usually was adequately met by an increase in coronary blood flow and/or compensated by a digoxin-induced reduction in ventricular volume resulting in reduction in myocardial wall tension.<sup>14</sup> In our patients, digoxin caused an increase in myocardial oxygen consumption. An increase in myocardial contractility would seem the most reasonable cause of this increased myocardial oxygen consumption, since no significant alterations in heart rate, preload, and afterload were noted. This increase in oxygen demand was satisfactorily compensated, as no significant change was noted in the measured coronary sinus oxygen content or in the measured lactate gradient across the myocardium.

The rate-pressure product is used frequently as an

indirect index of myocardial oxygen demand.<sup>24-26</sup> In our study, this index did not correlate with the myocardial oxygen consumption in the presence of digitalis.

Limitations of the technique for measuring coronary sinus blood flow used in this study have been summarized.<sup>16,27,28</sup> We feel this technique provides meaningful information regarding the magnitude and direction of changes in coronary blood flow when measured sequentially in the same patient. A potential technical criticism relates to the validity of comparative coronary sinus blood flow determinations by the thermodilution technique whenever right atrial pressure is elevated. In all patients, the positional stability of the catheter in the coronary sinus, and the absence of major reflux into the mouth of the coronary sinus was assessed as suggested by Mathey *et al.*<sup>29</sup>

The present study was done under clinical conditions in postoperative patients. Two patients were on chronic beta-adrenergic blockade before surgery. One patient received morphine sulfate subcutaneously 2.5 h before the study for postoperative pain. We cannot rule out the contribution of these medications to the hemodynamic and metabolic responses observed.

We must be cautious in judging the myocardial safety of digoxin in patients following myocardial revascularization from our data. Only one dose of the drug was studied; the effect of full digitalization in similar patients remains to be defined. Alterations in regional myocardial blood flow and regional myocardial metabolism may not be reflected in the overall global evaluation of myocardial metabolic function. Our study could not examine regional myocardial pathophysiology, and the effect of digoxin on these parameters remains to be determined.

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