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# *Myocardial Metabolism and Oxygenation in Man Awake and during Halothane Anesthesia*

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**Cardiac catheters were placed in seven healthy conscious patients so that aortic and left ventricular pressures (and the derivative), cardiac output (thermodilution) and myocardial blood flow (argon washin) could be measured. Blood was drawn for measurement of arterial blood-gas and arterial and coronary venous oxygen, glucose, lactate, pyruvate and fatty acid values. After induction of anesthesia by inhalation of halothane, the measurements were made during administration of low (0.70 per cent) and high (1.54 per cent) end-tidal halothane concentrations. Myocardial function decreased in a dose-related fashion without a change in heart rate. Myocardial blood flow and oxygen consumption were depressed in a similar manner. Myocardial oxygen extraction decreased and lactate did not change, suggesting that myocardial oxygenation was adequate. The heart rate–systolic blood pressure product correlated poorly with myocardial oxygen consumption. Systolic blood pressure and the contractile performance index dP/dt/IP were better correlated with myocardial oxygen consumption, but the value of the coefficient was still low. Without significant changes in heart rate, systolic blood pressure is the best correlate of myocardial oxygen consumption in healthy man during the myocardial depression produced by halothane. (Key words: Anesthetics, volatile: halothane. Heart: metabolism; blood flow, myocardial; cardiac output; myocardial function; oxygen consumption; vascular pressures. Metabolism: fatty acids; glucose; lactate; pyruvate.)**

THERE CAN BE LITTLE DOUBT that the depression in left ventricular function produced by halothane anesthesia in the dog[1,2] and pig[3] is accompanied by a marked decrease in myocardial oxygen consumption and demand. Consequently, there has been no evidence of myocardial tissue hypoxia even with markedly depressed cardiac function and myocardial blood flow in these species. Although we have demonstrated that the effect of halothane on left ventricular function in man is virtually identical to that seen in animals,[4] there has been no previous investigation of the relationship between this functional depression and myocardial metabolism in man. This study was designed to examine myocardial substrate metabolism and oxygenation in conscious nonmedicated patients and during low- and high-dose halothane anesthesia under carefully controlled conditions.

## Methods

Four men and three women, ranging in age from 27 to 47 years and in weight from 60.1 to 85.4 kg, were studied. All patients were scheduled for ligation and stripping of saphenous vein varicosities. Consequently, the femoral arterial puncture site (see below) could be directly inspected during the course of the operation. No patient gave a history or showed physical findings of any systemic disease. The protocol was approved by an ethics committee in the University of Göttingen composed of four medical school and two law school faculty members. The principles espoused in the declaration of Helsinki guided the committee.[5] Each patient signed an informed consent designed and approved by the committee.

After an overnight fast, the patients were brought to the anesthesia laboratory without premedication. An intravenous catheter was inserted in a forearm vein and a balanced salt solution (without glucose) was infused at a rate of 0.5 ml/kg/hour of fasting during the cardiac catheterization. The following catheters were placed percutaneously during local anesthesia with the aid of image-intensification fluoroscopy: through a brachial artery, a 7-Fr Goodale-Lubin catheter in the thoracic aorta; through a basilic or antecubital vein, a 7-Fr triple-lumen Edwards thermodilution catheter in the pulmonary artery; through a basilic or antecubital vein, a 7-Fr Goodale-Lubin catheter in the coronary sinus; through a femoral artery, a 5-Fr Millar catheter-tipped manometer in the left ventricle. Electrocardiographic electrodes were applied and rectal temperature was measured. After a rest period of 15 to 20 min, awake measurements and blood sampling were done. Blood loss from blood sampling at each measurement period was replaced with low-molecular-weight dextran. Throughout the experimental period, balanced salt solution was infused at a rate of 1 ml/kg/hr. Anesthesia was induced with halothane–air by face mask. Tracheal intubation was accomplished without the use of neuromuscular blocking drugs or topical anesthesia. Ventilation was controlled with an Engström® ventilator to maintain $Pa_{CO_2}$ near the awake values, guided by

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continuous airway carbon dioxide analysis. $F_{I_{O_2}}$ was adjusted to maintain $Pa_{O_2}$ near the awake value. External heating was used to maintain body temperature. End-tidal halothane concentration was measured with an ultraviolet analyzer (Hartmann and Braun). Before measurements were made, constant end-tidal halothane and carbon dioxide concentrations were maintained for at least 15 min. Halothane dose was adjusted to produce a 15–20 per cent decrease in mean aortic pressure at the low dose and a 20–40 per cent decrease at the high dose. Five patients received the low dose first, and two patients, the high dose. For each measurement period, vascular pressures were measured with the ventilator turned off; cardiac output values were calculated in triplicate; myocardial blood flow values were measured in duplicate, and aortic and coronary venous blood samples were withdrawn simultaneously. At the end of the second measurement period, the cardiac catheters were removed, hemostasis was assured, and the patients were moved into the operating room. There were no significant postanesthetic sequelae from the study.

Cardiac output was measured using the thermodilution technique (model 9510 cardiac output computer, Edwards Laboratories). Electrocardiogram, phasic and electronically integrated mean aortic pressure (Statham P23Db), left ventricular pressure (micro-tip TM PC350 Millar Instruments), dP/dt, and $CO_2$ concentration in expired air were recorded simultaneously on a six-channel UV-recorder (CHF Muller-Phillips). Left ventricular end-diastolic pressure and mean aortic diastolic pressure were obtained from the recordings. Coronary vascular resistance was calculated from the quotient of mean aortic pressure and myocardial blood flow. Myocardial blood flow was measured using the argon-washin technique from the coronary sinus after inhalation of a standard concentration of argon gas.[6]

Arterial blood-gas values were measured on standard electrodes (Radiometer—Copenhagen). Oxygen contents were calculated from measured oxygen saturation and hemoglobin concentrations (CO-oximeter 182, Instrumentation Laboratories) using 1.39 ml of oxygen/g hemoglobin as 100 per cent saturation. Blood glucose, lactate and pyruvate values were assayed enzymatically.[7] Nonesterified fatty acids were measured in plasma by the method of Duncombe.[8]

The Student $t$ test for paired samples was used to calculate $P$ values. $P < .05$ was assigned statistical significance.

TABLE 1. Controlled Variables

| | Awake | Halothane Anesthesia | |
|---|---|---|---|
| | | Low Concentration | High Concentration |
| Halothane (per cent end-tidal) | — | 0.70 ± 0.06 | 1.54 ± 0.12 |
| Body temperature (C) | 36.5 ± 0.1 | 36.2 ± 0.1 | 36.3 ± 0.1 |
| $pH_a$ | 7.39 ± 0.02 | 7.38 ± 0.02 | 7.39 ± 0.01 |
| $Pa_{CO_2}$ (torr) | 40 ± 1.3 | 38 ± 1.3* | 38 ± 0.9* |
| $Pa_{O_2}$ (torr) | 93 ± 4 | 92 ± 5 | 91 ± 4 |
| Base excess (mEq) | −1.0 ± 0.5 | −0.5 ± 0.4 | −1.2 ± 0.2† |
| Hemoglobin (g/dl) | 14.9 ± 0.6 | 14.5 ± 0.6* | 14.3 ± 0.5* |

* $P < 0.05$ *vs.* awake value.
† $P < 0.05$ *vs.* low concentration value.

## Results

End-tidal halothane concentrations averaged 0.7 per cent at the low level and 1.54 per cent at the high level (table 1). $Pa_{CO_2}$ and hemoglobin values were decreased slightly but significantly during halothane anesthesia. There was also a small but significant increase in base deficit with the high concentration of halothane. In general, the controlled variables were physiologically unchanged by halothane anesthesia.

Of the hemodynamic measurements, only heart rate did not change in a dose-related fashion during halo-

TABLE 2. Effect of Halothane on Hemodynamics

| | Awake | End-tidal Halothane 0.70 ± 0.06 Per Cent | End-tidal Halothane 1.54 ± 0.12 Per Cent |
|---|---|---|---|
| Heart rate(/min) | 72 ± 2 | 68 ± 2 | 68 ± 3 |
| MAP (torr) | 94 ± 3 | 80 ± 4* | 60 ± 6*† |
| LVEDP (torr) | 9.9 ± 0.5 | 11.3 ± 0.7* | 12.7 ± 0.7*† |
| LV dP/dt (torr/sec) | 1354 ± 28 | 1081 ± 73* | 885 ± 50*† |
| LV dP/dt/IP (l/sec) | 20.2 ± 0.6 | 17.5 ± 0.5* | 14.7 ± 0.5*† |
| CO (l/min) | 6.46 ± 0.47 | 5.66 ± 0.25* | 4.11 ± 4*† |
| SV (ml) | 90 ± 7 | 80 ± 6* | 59 ± 6*† |

MAP = mean aortic blood pressure; LVEDP = left ventricular end-diastolic blood pressure; LV dP/dt = maximum rate of rise of left ventricular pressure; LV dP/dt/IP = maximum rate of rise of left ventricular pressure/instantaneous left ventricular pressure; CO = cardiac output; SV = stroke volume.
* $P < 0.05$ *vs.* awake value.
† $P < 0.05$ *vs.* low-concentration value.

TABLE 3. Effects of Halothane on Myocardial Blood Flow and Oxygenation

| | Awake | End-tidal Halothane 0.70 ± 0.06 Per Cent | End-tidal Halothane 1.54 ± 0.12 Per Cent |
|---|---|---|---|
| MBF (ml/100 g/min) | 88 ± 3 | 74 ± 6* | 50 ± 4*† |
| $Ca_{O_2}$ (ml/dl) | 20.4 ± 0.8 | 19.7 ± 0.7* | 19.3 ± 0.8* |
| a − mv ($O_2$ ml) | 12.85 ± 0.65 | 11.71 ± 0.52* | 10.4 ± 0.55*† |
| $V_{O_2}$ (ml/100 g/min) | 11.3 ± 0.6 | 8.6 ± 0.7 | 5.15 ± 0.45*† |
| CVR | 1.07 ± 0.02 | 1.12 ± 0.06 | 1.23 ± 0.09* |
| $O_2$ extract (per cent) | 63 ± 2 | 60 ± 2 | 54 ± 1* |
| Lactate extract (per cent) | 18 ± 6 | 13 ± 5 | 14 ± 5 |

MBF = myocardial blood flow; $Ca_{O_2}$ = arterial blood $O_2$ content; a − mv = arterial–myocardial venous difference; $V_{O_2}$ = myocardial oxygen consumption; CVR = coronary vascular resistance; $O_2$ extract = myocardial oxygen extraction (a − v/a); lactate extract = myocardial lactate extraction.
* $P < 0.05$ *vs.* awake value.
† $P < 0.05$ *vs.* low concentration value.

thane anesthesia (table 2). Left ventricular filling pressure (LVEDP) increased progressively, and all measurements of left ventricular function decreased (table 2). Myocardial blood flow and oxygen consumption also decreased in concert with left ventricular function (table 3). Myocardial oxygen extraction actually decreased, as did arterial oxygen content and the arterial–coronary venous oxygen difference. There was no significant change in myocardial lactate extraction.

Arterial lactate concentration was increased during halothane anesthesia, but there was no significant difference between the low and high halothane concentrations (table 4). The other substrates were not significantly affected by halothane anesthesia, except that uptake decreased during administration of the high concentration as a result of the decrease in myocardial blood flow (table 4).

## Discussion

To our knowledge there has been no previously published report of the effect of halothane (or any inhalation anesthetic) on myocardial blood flow and oxygen consumption in man. Experiments in dogs[1,2,-9-11] and pigs[3] have generally indicated that myocardial blood flow and oxygen consumption decrease together with ventricular function and the accepted determinants of myocardial oxygen consumption. This correlation suggests that the normal metabolic control of coronary blood flow and myocardial oxygenation is present during halothane anesthesia.[12] Studies from the laboratory of one of the authors (RGM)[1-3] have shown no change in the relationship between aortic blood pressure and myocardial blood flow (or calculated coronary vascular resistance) during halothane anesthesia. However, Saito *et al.*,[9] Smith *et al.*,[11] and Wolff *et al.*[13] have reported that coronary vascular resistance was increased with high concentrations of halothane. Inasmuch as the direct effect of halothane on coronary vascular smooth muscle is dilatory,[14] an increase in coronary vascular resistance can only indi-

TABLE 4. Effects of Halothane on Myocardial Metabolism

| | Awake | End-tidal Halothane 0.70 ± 0.06 Per Cent | End-tidal Halothane 1.54 ± 0.12 Per Cent |
|---|---|---|---|
| Glucose | | | |
| Arterial blood concentration (mg/dl) | 104 ± 5 | 105 ± 6 | 103 ± 7 |
| a − mv (mg/dl) | 3.6 ± 0.8 | 3.3 ± 1.9 | 2.4 ± 0.7* |
| Uptake (mg/100 g/min) | 3.2 ± 0.7 | 2.3 ± 1.3 | 1.2 ± 0.3* |
| Nonesterified fatty acids | | | |
| Arterial blood concentration (mEq/l) | 1.37 ± 0.30 | 1.56 ± 0.42 | 1.53 ± 0.42 |
| a − mv (mEq/l) | 0.23 ± 0.05 | 0.26 ± 0.06 | 0.24 ± 0.06 |
| Uptake (mEq/100 g/min) | 0.020 ± 0.004 | 0.018 ± 0.004 | 0.012 ± 0.003* |
| Lactate | | | |
| Arterial blood concentration (mg/dl) | 7.24 ± 1.7 | 8.86 ± 1.03* | 10.46 ± 2.03* |
| a − mv (mg/dl) | 1.24 ± 0.4 | 1.34 ± 0.6 | 1.65 ± 0.65 |
| Uptake (mg/100 g/min) | 1.07 ± 0.34 | 0.92 ± 0.4 | 0.73 ± 0.26* |
| Pyruvate | | | |
| Arterial blood concentration (mg/dl) | 0.60 ± 0.04 | 0.79 ± 0.09* | 0.67 ± 0.07 |
| a − mv | 0.12 ± 0.06 | 0.14 ± 0.05 | 0.10 ± 0.03 |
| Uptake (mg/100 g/min) | 0.10 ± 0.05 | 1.11 ± 2.04 | 0.04 ± 0.01* |

a − mv = arterial–myocardial venous difference.
* $P < 0.05$ *vs.* awake value.

cate a marked decrease in myocardial metabolic demands. Whether the calculated coronary vascular resistance increases or remains constant depends on the magnitude of the metabolic depression. In the situation reported in this study, coronary vascular resistance increased significantly during administration of the high concentration of halothane (table 3). That this was a result of decreased metabolic demand and not direct vasoconstriction is indicated by the decrease in oxygen extraction and maintenance of lactate uptake. Certainly, there was no evidence that myocardial oxygen supply was inadequate for the demand.

Other anesthetic techniques also appear to effect changes in myocardial (coronary) blood flow and oxygen consumption through changing myocardial oxygen demand in man. In the first published report of the effect of anesthesia on myocardial perfusion and oxygenation in man, spinal anesthesia produced decreases in myocardial blood flow and myocardial oxygen consumption that were proportional to the decreases seen in systemic blood pressure.[15] Unchanged myocardial oxygen and lactate extraction ratios led these investigators to conclude that myocardial oxygenation was unimpaired. The series of investigations from this laboratory on the effects of intravenous anesthetics on left ventricular dynamics and myocardial blood flow and metabolism has also indicated that the changes in coronary blood flow and oxygen consumption were related to the hemodynamic changes produced. The increased heart rate seen with most induction agents was coupled with increased coronary blood flow and myocardial oxygen consumption and decreased coronary vascular resistance.[16] Ketamine also increased contractile performance and aortic blood pressure, with correspondingly greater increases in myocardial blood flow and oxygen consumption.[17] A combination of droperidol and fentanyl[18] and the investigational induction agent, etomidate,[19] produced little hemodynamic change and hence, minimal changes in coronary blood flow and oxygen consumption. In every instance, there was little change in oxygen or lactate extraction, suggesting that the changes in coronary blood flow were appropriate for the oxygen demand of these hearts (H. Sonntag, unpublished data).

The measurement of myocardial (coronary) blood flow and oxygen consumption is difficult in man. Consequently, it would be useful if some easier hemodynamic measurements could be found that would reflect one or the other. In the previous investigation of the effect of halothane on the left ventricular function in man,[4] we referred to a complex hemodynamic method of estimating myocardial oxygen consumption. Unfortunately, the components of this formula

TABLE 5. Correlation of Myocardial Oxygen Consumption with Hemodynamic Values in Patients Conscious and Anesthetized with Halothane

| | Awake | Anesthetized |
|---|---|---|
| Heart rate | −.015 | .088 |
| Systolic blood pressure | .357 | .6342* |
| dP/dt/LVP | −.078 | .5622* |
| HR × SBP | .283 | .499 |
| dP/dt/IP × SBP | .140 | .648* |
| HR × SBP × dP/dt/IP | .134 | .559* |

HR = heart rate; SBP = systolic blood pressure; dP/dt/IP = left ventricular dP/dt/instantaneous left ventricular pressure.
* $P < 0.05$.

are as difficult to obtain in man as are myocardial blood flow and oxygen consumption. In particular, measurement of left ventricular dP/dt and heart volumes (end-systolic and diastolic) requires sophisticated and invasive techniques which, for the latter, were not even available for this investigation. For accurate estimates of the contribution of contractile performance and wall tension, such measurements are necessary. However, excellent correlation has been shown in man between myocardial oxygen consumption and two easily obtained determinants, heart rate and systolic blood pressure. In healthy volunteers,[20] and in patients with ischemic heart disease,[21] the heart rate–systolic blood pressure product (rate–pressure product) correlated well with measured myocardial oxygen consumption (r values of 0.8620 and 0.8321). Although this relationship has been used in studies in anesthetized man,[22–24] heretofore there has been no documentation of the correlation in man during anesthesia. In our group of healthy patients, the correlation was considerably less satisfactory. Neither awake nor during halothane anesthesia was there an acceptable or even statistically significant relationship between the rate–pressure product and myocardial oxygen consumption (table 5 and fig. 1), even though rate–pressure product decreased significantly and in a dose-related fashion during halothane anesthesia (awake 8918.4 ± 380; halothane, 0.7 per cent 6935.9 ± 580; halothane, 1.54 per cent, 5262.9 ± 747). The decrease was entirely the result of the decrease in systolic blood pressure, since there was no change in heart rate (table 2). In the studies referred to above, changes in myocardial oxygen consumption and cardiac dynamics were obtained with static and dynamic exercise. Heart rates were increased markedly under these circumstances and, in fact, were as well correlated with myocardial oxygen consumption as the rate–pressure product (correlation coefficients of 0.80[20] and 0.79[21]). As might be expected, there was no correlation between heart rate and myocardial oxy-

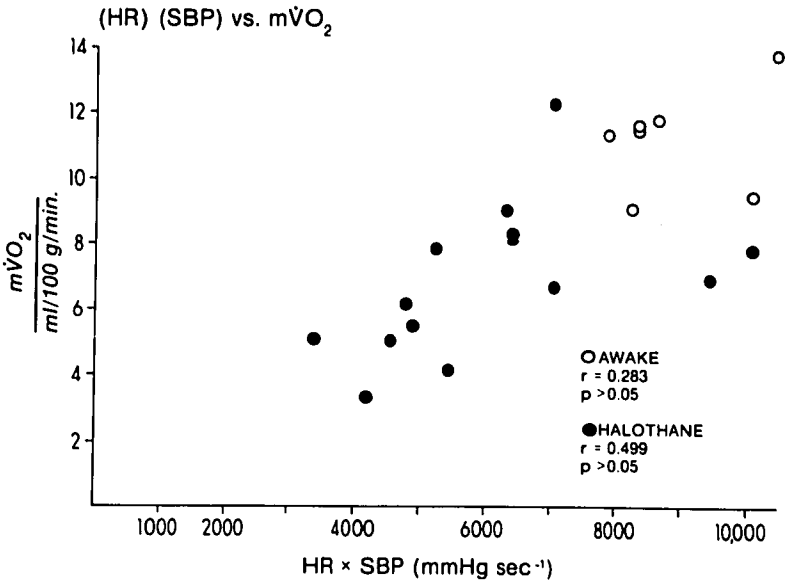


FIG. 1. Correlation between myocardial oxygen consumption and heart rate–systolic blood pressure product. $m\dot{V}_{O_2}$ = myocardial oxygen consumption; HR × SBP = heart rate–systolic blood pressure product.

gen consumption in our group of patients (table 5). Correlation between systolic blood pressure and myocardial oxygen consumption was statistically significant, but the coefficient was considerably lower than seen with exercise in awake subjects (table 5 and fig. 2). Since the predominant cardiodynamic effect of halothane is to decrease contractile performance of the heart, we thought that an estimate of this aspect of cardiovascular function might prove to be an acceptable correlate. Although the relationship of maximum rate of rise of left ventricular pressure/instantaneous left ventricular product (dP/dt/IP) to myocardial oxygen consumption was significant, as with the systolic pressure, the relatively low coefficient leaves some doubt as to the usefulness of the relationship (table 5 and fig. 3). The correlation between the product of heart rate, systolic blood pressure, and dP/dt/IP was about the same as that for dP/dt/IP, and less than that for systolic blood pressure (table 5). Hence, the product of dP/dt/IP and systolic blood pressure correlated no better than systolic blood pressure alone (table 5 and fig. 4). Consequently, it appears that systolic blood pressure is a better correlate of myocardial oxygen consumption during halothane anesthesia without surgical intervention in man than rate–pressure product. Adding a contractile performance index did not change the correlation. Of course, with operation, blood loss, etc., changes in heart rate might occur and modify the relationship.

The only arterial substrate that changed during

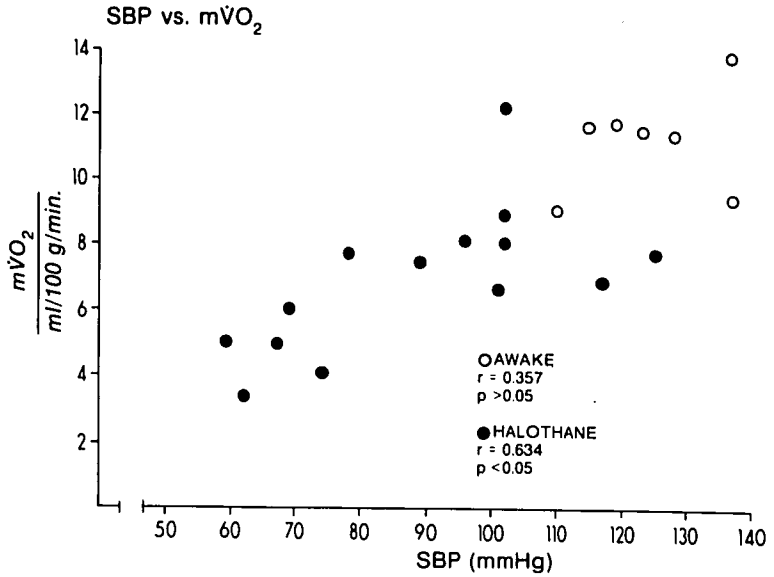


FIG. 2. Correlation between myocardial oxygen consumption and systolic blood pressure. $m\dot{V}_{O_2}$ = myocardial oxygen consumption; SBP = systolic blood pressure product.

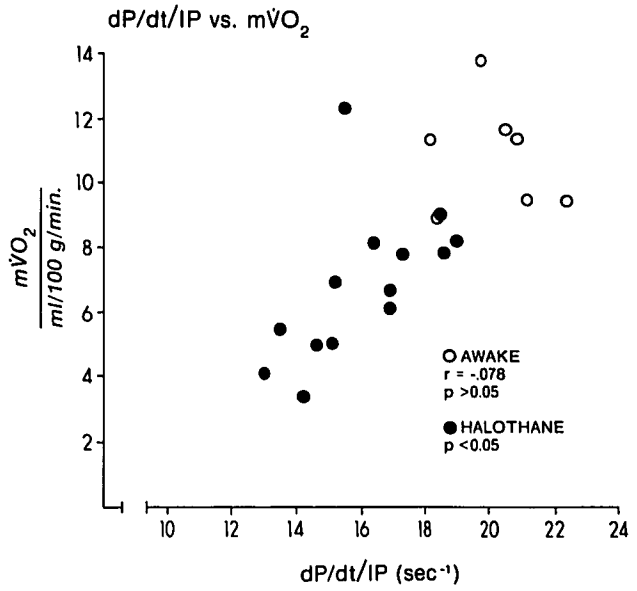


FIG. 3. Correlation between myocardial oxygen consumption and a contractility index, left ventricular dP/dt/IP. $m\dot{V}_{O_2}$ = myocardial oxygen consumption; dP/dt/IP = maximum rate of rise of left ventricular pressure/instantaneous left ventricular pressure.

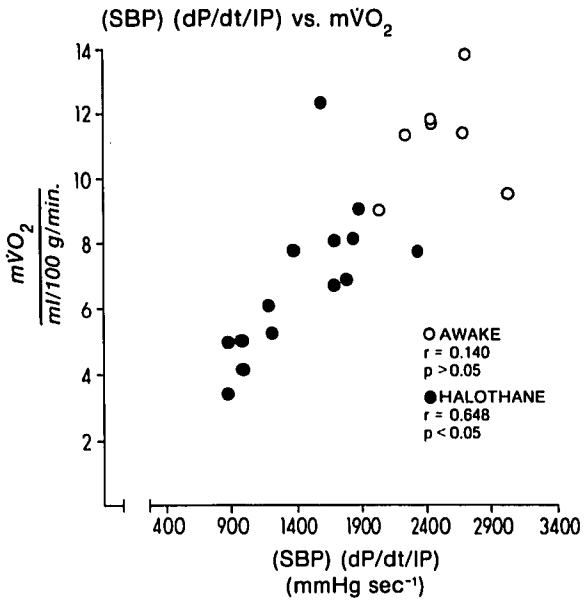


FIG. 4. Correlation between myocardial oxygen consumption and systolic blood pressure–myocardial contractility index product. $m\dot{V}_{O_2}$ = myocardial oxygen consumption; SBP (dP/dt/IP) = systolic blood pressure–myocardial contractility product.

halothane anesthesia was lactate. The increase in arterial lactate values was also seen in the chronic dog studies referred to above,[2] and the possible mechanisms were discussed in that publication. We have found an increase in venous blood lactate levels during halothane anesthesia in association with another study[25] (unpublished results). Lest it appear that the increase in lactate is specific for halothane, it must be noted that the same increase has been seen with enflurane,[26] methoxyflurane, fluroxene and isoflurane in dogs, and methoxyflurane in man (unpublished data). Consequently, it is possible that the effect is nonspecific and related to CNS depression or some alteration of the autonomic nervous system. Hyperglycemia has been seen previously during halothane anesthesia (without surgical intervention),[25] but the observation is not universal. Although arterial glucose levels were unchanged in this study, just as they had been in the dog studies,[2] the awake levels were high. As in the dog study, myocardial glucose uptake appeared to follow the functional depression of the heart, being significantly less at the high halothane concentration. In a previous study in man, venous blood nonesterified fatty acid values also increased significantly during halothane anesthesia.[25] Again, the conscious levels in the present study were high. Although the hemodynamic data in our patients do not suggest sympathetic nervous system activity, it is possible that the relatively high awake glucose and nonesterified fatty acid levels were a result of some adrenergic stimulation.[27] Consequently, increased lipolysis and glycogenolysis from sympathetic nervous system stimulation or from decreased insulin secretion related to halothane induction would not be apparent.[25]

In conclusion, the effects of halothane on myocardial oxygenation and metabolism in man are similar to those seen in the dog. In both species, myocardial blood flow and oxygen consumption appear to be a function of the hemodynamic changes produced by halothane. Unlike the analogous situation in exercising man, there is a poor correlation between myocardial oxygen consumption and heart rate–blood pressure product during halothane anesthesia, perhaps because there was no change in heart rate. Changes in arterial blood pressure and contractile function of the heart were more closely related to myocardial oxygen consumption, but the correlation was still rather weak. At present, there does not appear to be a good, simple, clinical correlate of myocardial oxygen demand during halothane anesthesia in human beings when heart rate is not changed.

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