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Validation of Myocardial Oxygen Demand Indices in Patients Awake and during Anesthesia

Andreas Hoeft, M.D., Hans Sonntag, MD,† Heidrun Stephan, MD,* Dietrich Kettler, M.D.‡*

An important guideline for anesthesia in patients with ischemic heart disease is the effect on myocardial oxygen demand. Therefore, this investigation evaluated commonly used myocardial oxygen demand formulas for clinical application. The study was performed on patients undergoing coronary bypass surgery (n=62). Measurements of standard hemodynamics were obtained before and after induction of anesthesia, as well as during sternotomy and after surgery. Coronary blood flow was determined by the argon wash-in technique. In 15 patients, a left ventricular tip manometer was used to accurately assess the first derivative of left ventricular pressure time course. The following indices of left ventricular oxygen demand were calculated: 1) rate pressure product (RPP); 2) tension time index (TTI); 3) pressure work index (PWI) according to the methods of Rooke; and 4) additive parameter (E_g), according to the methods of Bretschneider. All hemodynamic indices of myocardial oxygen demand showed moderate correlation with myocardial oxygen uptake ($M\dot{V}_{O_2}$) (RPP: r = 0.77; TTI: r = 0.79; PWI: r = 0.79; E_g: r = 0.71). On the average, PWI and E_g led to an underestimation of $M\dot{V}_{O_2}$ in patients. The constants of the PWI and E_g formulas, which have been developed based on animal experiments, therefore are not directly applicable to clinical conditions. New constants have been derived for PWI by multiple linear regression analysis of the data in the current investigation. The PWI formula thereby was modified for clinical application ($PWI_{mod} = K_1 P_{syst} HR + K_2 [0.8 P_{syst} + 0.2 P_{diast}] CI$; $K_1 = 8.37 \cdot 10^{-4}$, $K_2 = 8.0 \cdot 10^{-6}$; where P_{syst} = systolic blood pressure, HR = heart rate; P_{diast} = diastolic blood pressure, and CI = cardiac index) and retrospectively showed reasonably good correlation with $M\dot{V}_{O_2}$ (r = 0.84) in patients. The 95% limits of agreement between $M\dot{V}_{O_2}$ and PWI_{mod} were ± 3.96 ml · min^{-1} · 100 g^{-1}. The authors conclude from the current investigation that hemodynamic indices of myocardial oxygen demand derived from animal experiments cannot be applied to humans without modification. (Key words: Heart: myocardial performance; oxygen consumption; pressure work index; rate pressure product; tension time index.)

IN PATIENTS with coronary artery disease, oxygen delivery to the heart is limited because of impaired coronary blood supply. Therefore, an important guideline for anesthesia, as well as any cardiovascular therapy, is the effect on myocardial oxygen demand.

Routine monitoring of myocardial oxygen uptake ($M\dot{V}_{O_2}$) is not practical in patients, because measurement of $M\dot{V}_{O_2}$ requires considerable effort, including a coronary sinus catheter, analysis of arterial and coronary sinus blood samples, and measurements of myocardial blood flow. Therefore, clinical therapy often must be based on the estimation of myocardial oxygen demand from hemodynamic variables.[1,2] Most investigations comparing myocardial oxygen demand indices with direct measurements of $M\dot{V}_{O_2}$ were performed on animals, and only a few data include measurements of coronary blood flow in humans.[3,4] Recently, Rooke and Feigl have shown in dogs that the pressure work index (PWI) provides a good estimation of $M\dot{V}_{O_2}$ and that this index is superior to the rate pressure product (RPP).[5,6] Kahles *et al.*[4] directly measured oxygen uptake in awake patients undergoing cardiac catheterization and found good agreement between measured oxygen uptake and the oxygen demand calculated according to an additive formula developed by Bretschneider[7,8] (E_g).

However, our work using measurements of coronary blood flow by the inert gas dilution technique and the recent findings of Hasenfuss *et al.*[3] provide evidence that the formulas developed for animal data might not be applicable to human data without modification. Therefore, the aim of the current investigation was to validate common indices for myocardial oxygen demand in patients during the awake state and during anesthesia. Four formulas were investigated: 1) the RPP, which is used very often clinically to estimate changes of myocardial oxygen demand; 2) the tension time index (TTI), which has been proposed to be superior to RPP; 3) the formula of Bretschneider (E_g), which requires a highly invasive left ventricular tip manometer for assessment of dP/dt_{max} but has proved to be a valuable tool in our experimental laboratories; and 4) the PWI of Rooke and Feigl,[5] (PWI), which is based on measurements of cardiac output and blood pressure only, and therefore could be more appropriate for clinical application.

Materials and Methods

The study was approved by the Committee for Medical Ethics of the University of Göttingen. Each patient gave fully informed consent during the preoperative visit. All patients were scheduled for coronary bypass surgery; no patient had a history of congestive heart failure or valvular disease. Each patient had an ejection fraction greater than 50%.

* Staff Anesthesiologist.

† Professor of Anesthesiology.

‡ Professor of Anesthesiology; Head of Department of Anesthesiology.

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Address reprint requests to Dr. Hoeft: Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin, der Universität Göttingen Robert-Koch-Str. 40, D-3400 Göttingen, Germany.

The patients received flunitrazepam 2 mg orally 1 h before they were sent to the operating room. When leaving the ward, they received promethazine 50 mg and piritramide 15 mg intramuscularly (im). On arrival of the patient in the operating room, ECG leads were attached. The patients received a pulmonary arterial catheter (7 French, through the left antecubital vein), a central venous catheter (through the peripheral vein), and a coronary sinus catheter (6 French, through the right internal jugular vein). The radial artery was cannulated on the nondominant side for measurement of arterial pressures and blood sampling. In 15 patients, a catheter tip manometer (PC 350, Millar Instruments) inserted through the femoral artery was used for measurement of left ventricular dP/dt_{max}. ECG and all pressures were recorded continuously on a ten-channel recorder (Hellige GmbH).

General anesthesia was induced with fentanyl 7 $\mu g \cdot kg^{-1}$, etomidate 0.3 $mg \cdot kg^{-1}$, and pancuronium 8 mg to facilitate endotracheal intubation. Ventilation was maintained with an FI_{O_2} of 0.30–0.50 in air or in N_2O when systolic blood pressure exceeded 100 mmHg. All patients had maintenance doses of calcium channel blockers (nifedipine 20–60 mg/day or diltiazem 120–180 mg/day) and nitrates (40–160 mg/day); the last dose was administered the morning of surgery.

Patient Measurements

Measurements were performed before and after induction of anesthesia, as well as during sternotomy and sternal spread. Cardiac output was determined by thermodilution using the pulmonary artery catheter and at least three to five injections of 10 ml ice-cold saline. Myocardial blood flow was determined by the wash-in inert gas dilution technique, with inhalation of argon in oxygen and continuous sampling of arterial and coronary venous blood by a syringe pump (coefficient of variation, 5.1%).[9] The sampling time for coronary blood flow measurement was 5 min. Immediately before and after myocardial blood flow measurement, samples were obtained from the radial artery and coronary sinus. Samples were analyzed for hemoglobin content, oxygen saturation (CO-oximeter IL 282), and oxygen content (Lex-O_2-Con®, Lexington).

Because myocardial blood flow per 100 g left ventricular mass is obtained directly by the inert gas method for measurement of myocardial blood flow, myocardial oxygen consumption per 100 g can be calculated easily as the product of blood flow and the arterial coronary − venous oxygen content difference.

Calculations

For each measured steady state, the following four indices of myocardial oxygen demand were calculated:

1. Rate pressure product (RPP): $RPP = P_{syst}HR$
2. Tension time index (TTI): $TTI = P_{syst}t_eHr$
3. Pressure work index (PWI): $PWI = C_0 + C_1 + C_2$

$C_0 = K_0$ $\quad K_0 = 1.43$

$C_1 = K_1P_{syst}HR$ $\quad K_1 = 4.08 \cdot 10^{-4}$

$C_2 = K_2(0.8\ P_{syst} + 0.2P_{diast}) \times SV \cdot HR \cdot BW^{-1}$ $\quad K_2 = 3.25 \cdot 10^{-4}$

$C_0 - C_3$: Components of total myocardial energy demand

$K_0 - K_3$: Constants derived from animal experiments

4. Bretschneider parameter (E_g): $E_g = E_0 + E_1 + E_2 + E_3 + E_4$

$E_0 = K_0$ $\quad K_0 = 0.7$

$E_1 = K_1t_{QT}HR$ $\quad K_1 = 3.0 \cdot 10^{-2}$

$E_2 = K_2P_{syst}ESV^{1/2}t_eHR$ $\quad K_2 = 1.4 \cdot 10^{-3}$

$E_3 = K_3dP/dt_{max}HR$ $\quad K_3 = 1.2 \cdot 10^{-4}$

$E_4 = K_4dP/dt_{max}{}^{3/2}HR$ $\quad K_4 = 8.0 \cdot 10^{-9}$

$ESV = K_{ESV}P_{syst}dP/dt_{max}{}^{-1/2}$ $\quad K_{ESV} = 11.0$

E_0: energy required for basal metabolism

E_1: energy required for electrophysiological activities

E_2: energy required for maintenance of tension during ejection phase

E_3: energy required for development of tension during isovolumic contraction

E_4: energy required for calcium movements across the membranes

ESV: estimated endsystolic volume per 100 g ventricular weight

$K_{0-4,ESV}$: constants derived from animal experiments

where P_{syst} = systolic blood pressure; dP/dt_{max} = maximum of first derivative of left ventricular pressure time course; P_{diast} = diastolic blood pressure; HR = heart rate; t_e = systolic ejection time; t_{QT} = duration of electrical systole (QT time in ECG); BW = body weight; and SV = stroke volume.

Statistics

The four calculated indices (RPP, TTI, PWI, E_g) were analyzed by linear regression analysis in comparison with measured oxygen uptake. PWI and E_g are designed to estimate myocardial oxygen demand in milliliters of oxygen per minute per 100 g tissue. It is possible, therefore, to regard the calculated values of PWI and E_g as an alternative method to the direct determination of $M\dot{V}_{O_2}$. The data thus can be analyzed by the statistical methods suggested by Bland and Altman for assessing agreement between two methods of clinical measurement.[10,11] The difference between the two methods is plotted against the mean. The mean difference and the standard deviation

TABLE 1. Hemodynamic Data

	n	P_{LV} (mmHg)	dP/dt_{max} (mmHg·s^{-1})	HR (beats per min)	CI (l·m^{-2})
Awake	62	140 ± 17.4	1403 ± 203*	71 ± 12.8	3.41 ± 0.56
After induction	50	115 ± 17.1	1306 ± 379†	82 ± 20.6	3.00 ± 0.71
Sternotomy	50	138 ± 26.2		79 ± 16.6	2.72 ± 0.93
End of surgery	30	126 ± 23.3		103 ± 15.6	2.98 ± 0.76
	n	MBF (ml·min^{-1}·100 g^{-1})	art.$_{O_2}$ (mg·100 ml^{-1})	$AVDO_2$ (ml·100 ml^{-1})	
Awake	62	104 ± 24.1	17.7 ± 1.7	11.6 ± 1.4	
After induction	50	94 ± 37.9	17.7 ± 1.9	11.2 ± 1.7	
Sternotomy	50	111 ± 41.2	16.7 ± 1.9	11.3 ± 2.1	
End of surgery	30	139 ± 38.6	14.7 ± 2.1	9.3 ± 1.3	

Data are presented as mean ± standard deviation.
P_{LV} = left ventricular systolic pressure; dP/dt_{max} = maximum of left ventricular pressure increase; HR = heart rate; CI = cardiac index; MBF = myocardial blood flow per 100 g tissue; art.$_{O_2}$ = arterial O_2 content; AVD_{O_2} = arterio–coronary venous O_2 content difference.
* n = 15.
† n = 14.

of the mean difference are calculated. The limits of agreement between both methods is given by the mean difference ± two standard deviations. Ninety-five percent of all differences lie within these limits. In contrast to the calculation of correlation coefficients, this approach is independent of the range of the analyzed data. The 95% confidence intervals for the mean differences were calculated based on a t-distribution, according to the suggestion of Bland and Altman.

Results

Although the patients had received flunitrazepam, promethazine, and piritramide as preanesthetic medication, a slight elevation in blood pressure was found during the awake state. In most patients, induction of anesthesia was associated with a slight reduction of left ventricular systolic pressure and cardiac output (table 1). In some patients heart rate significantly increased during intubation (maximum, 136 beats per min), and in some patients high blood pressure peaks were observed during sternotomy (maximum systolic pressure (P_{syst}), 210 mmHg). In 15 patients, measurements of dP/dt_{max} were obtained during the awake state and after induction of anesthesia. Although blood pressures during the awake state were increased, relatively low values for dP/dt_{max} were found. Measurements of dP/dt_{max} during surgical stimulation (*i.e.*, during sternotomy) were not performed, to avoid complications that might result from the tip manometer catheter during this procedure.

The correlations of $M\dot{V}O_2$ with RPP, TTI, PWI, and E_g are shown in figures 1–4. No major differences of the correlation coefficients were found (r = 0.77, 0.79, 0.79, and 0.71 for RPP, TTI, PWI, and E_g, respectively). In

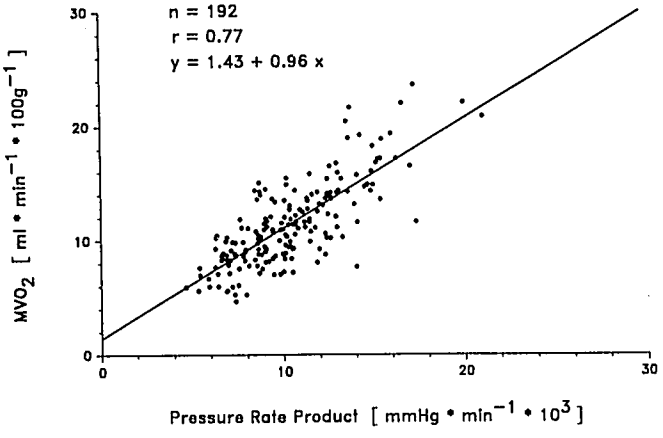

FIG. 1. Linear regression analysis of rate pressure product (RPP) and measured myocardial oxygen uptake ($M\dot{V}O_2$). Data were obtained in patients during awake state, after induction of anesthesia and during sternotomy.

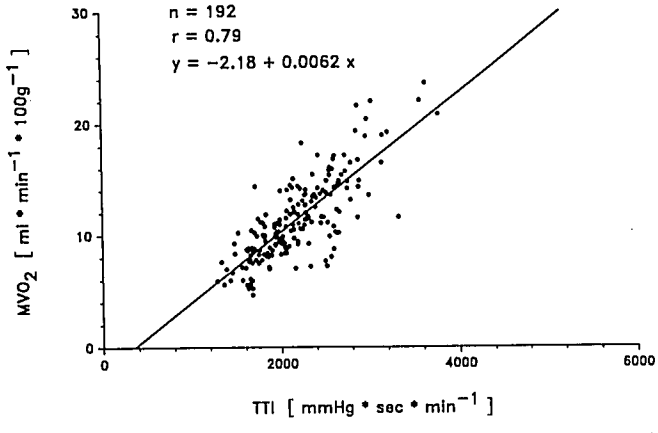

FIG. 2. Linear regression analysis of tension time index (TTI) and measured myocardial oxygen uptake ($M\dot{V}O_2$). Data were obtained in patients during awake state, after induction of anesthesia, and during sternotomy.

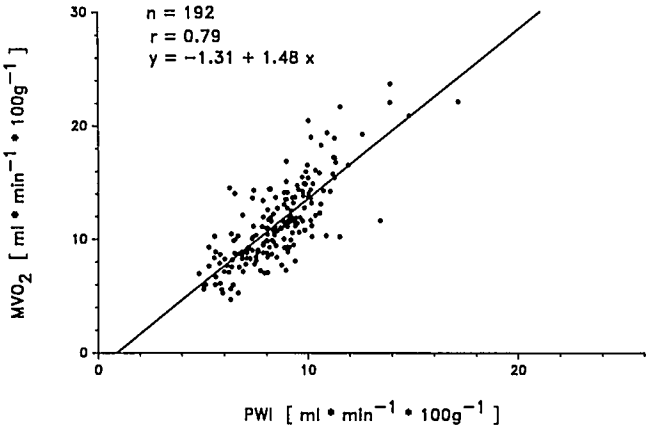

FIG. 3. Linear regression analysis of predicted myocardial oxygen demand calculated by the pressure work index (PWI) and measured myocardial oxygen uptake ($M\dot{V}_{O_2}$). Data were obtained in patients during awake state, after induction of anesthesia, and during sternotomy. The slope of the regression line (1.48) indicates a systematic underestimation of $M\dot{V}_{O_2}$ by PWI in patients.

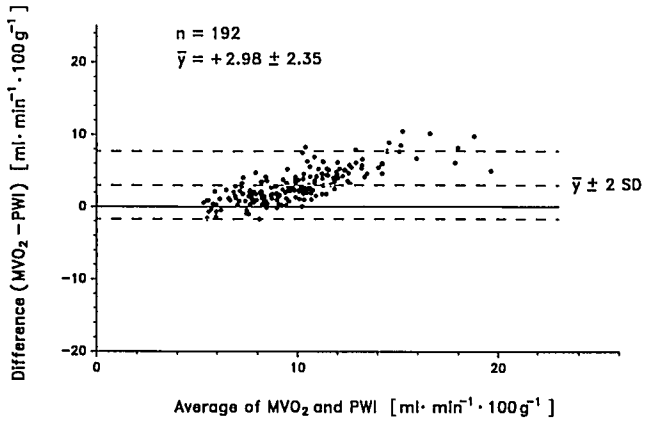

FIG. 5. Comparison of pressure work index (PWI) and measured myocardial oxygen uptake ($M\dot{V}_{O_2}$) according to the method of Bland and Altman.[10] The difference between $M\dot{V}_{O_2}$ and PWI is plotted on the ordinate against the mean of $M\dot{V}_{O_2}$ and PWI on the abcissa. The mean difference (2.98 ml · min^{-1} · 100 g^{-1}) and the limits of agreement (± 2 standard deviations) are depicted by dashed lines. The difference between $M\dot{V}_{O_2}$ and PWI is not constant over the entire range but increases with increasing oxygen demand.

general, the measured $M\dot{V}_{O_2}$ was greater than the $M\dot{V}_{O_2}$ calculated by PWI or by E_g. The slopes of the linear regression lines (1.48 and 5.0) indicate that the systematic error of estimating $M\dot{V}_{O_2}$ by PWI or E_g is a proportional one rather than an additive one.

The agreement of PWI and E_g with $M\dot{V}_{O_2}$ also was analyzed by the method of Bland and Altman[10] (figs. 5 and 6). It can be demonstrated clearly that $M\dot{V}_{O_2}$ is underestimated by PWI as well as by E_g: The mean differences are 2.89 and 7.83 ml · min^{-1} · 100 g^{-1}, respectively. The 95% confidence intervals based on the t-distribution for these mean differences are 2.56 to 3.22 ml · min^{-1} · 100 g^{-1} for PWI and 6.19 to 9.47 ml · min^{-1} · 100 g^{-1} for E_g. Therefore, the underestimation of $M\dot{V}_{O_2}$ by PWI and E_g is statistically significant ($P < 0.05$). Furthermore, it can be observed that the deviation between the calculated indices and the measured values of $M\dot{V}_{O_2}$ increases with higher values of oxygen uptake.

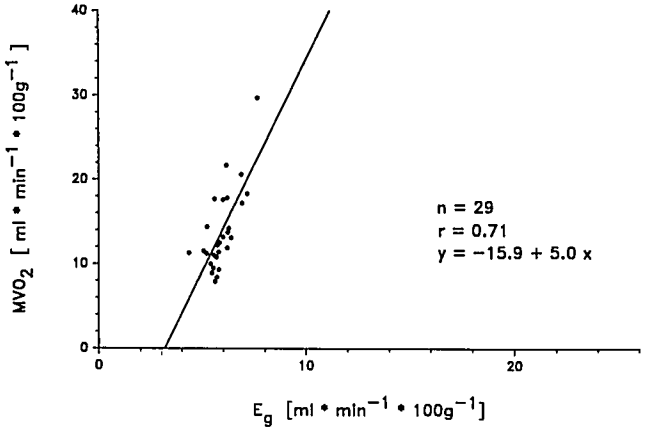

FIG. 4. Linear regression analysis of predicted myocardial oxygen demand calculated by the Bretschneider[7,8] formula (E_g) and measured myocardial oxygen uptake ($M\dot{V}_{O_2}$). Data were obtained in patients during awake state, after induction of anesthesia, and during sternotomy. E_g clearly underestimates $M\dot{V}_{O_2}$ in patients.

Discussion

A major objective of the current investigation was to evaluate commonly used indices of myocardial oxygen demand for clinical application. It was found that all indices under investigation showed moderate correlation with directly measured oxygen uptake of the heart. Furthermore, with the use of the empiric constants derived in animal experiments, E_g and PWI underestimated $M\dot{V}_{O_2}$ to a considerable extent.

Indices for Estimation of Myocardial Oxygen Demand

Several formulas have been suggested in the literature for estimation of myocardial energy demand and $M\dot{V}_{O_2}$. In 1895, Frank§ developed a theoretic approach to describe the total effort of the heart. His formula represented a sum of five major components (fig. 7): 1) the energy requirements for pressure volume work done by the ventricle during systole (fig. 7, I) subtracted by the pressure volume work received by the ventricle during diastole (fig. 7, II); 2) the kinetic work of the heart for

§ Frank O: Die Grundform des arteriellen Pulses. Z Biol 36:483–526, 1895.

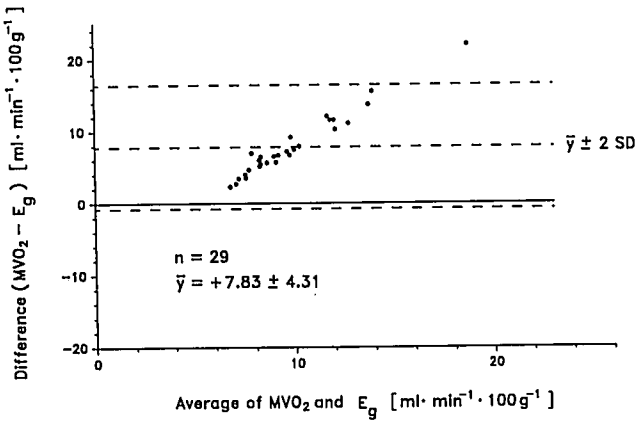

FIG. 6. Comparison of the Bretschneider[7,8] formula (E_g) and measured myocardial oxygen uptake ($M\dot{V}_{O_2}$) according to the method of Bland and Altman.[10] The difference between $M\dot{V}_{O_2}$ and E_g is plotted on the ordinate against the mean of $M\dot{V}_{O_2}$ and E_g. The mean difference (7.83 ml · min^{-1} · 100 g^{-1}) and the limits of agreement (±2 standard deviations) are depicted dashed lines. A large difference between both methods tends to increase with increasing $M\dot{V}_{O_2}$.

the blood leaving the ventricle during systole (fig. 7, III), which is also diminished by the kinetic energy of the blood entering into the ventricle during diastole (fig. 7, IV); 3) the energy requirements for intramyocardial frictional resistances during contraction (fig. 7, V); 4) requirements for changes of internal mechanical energy (fig. 7, VI); and 5) energy that is combusted for heat generated by metabolism (fig. 7, VII). Although Frank's early approach is interesting, the resulting formula is obviously more theoretic and not applicable to clinical or experimental measurements.

Later, in 1912, a more practical suggestion was made by Rhode, who considered the product of heart rate and systolic blood pressure to be an appropriate indirect index of myocardial oxygen demand.[12] In contrast to Frank's theoretic formula, this so-called "rate pressure product" was much more attractive for clinical application because blood pressure and heart rate can be measured noninvasively. In the following decades, the RPP has been advocated by several authors, with slight modifications.[13,14] It also might be assumed that external cardiac work is also related to myocardial energy turnover. However, it was shown very early that external cardiac work alone does not correlate with myocardial oxygen demand. Evans and Matsuoka as well as others demonstrated that the oxygen cost of the same increase in "flow work" was less than the same increase in "pressure work."[15,16] The efficiency of myocardial performance therefore is not constant, but decreases with pressure load. Evans and Matsuoka concluded that the tension set up on contraction—not the external pressure volume work—should be related to the metabolism of the contractile tissue. Subsequently, several studies focused on indices of $M\dot{V}_{O_2}$ based on wall tension or wall force (*i.e.*, TTI,[17] contractile element work,[18] estimated wall tension,[19] and the triple product[20]). It soon became evident that, in addition to wall tension, additional factors influence myocardial energy demand. Some investigators found that myocardial inotropism and contractile state are important determinants of myocardial oxygen demand.[21] On the other hand, it was shown in skeletal and papillary muscle experiments that the process of muscle shortening requires an extra amount of oxygen, even if contractility and developed tension are constant. Some investigators[22,23] have found this so-called "Fenn effect" to be relevant for the intact heart, but this could not be verified by others.[8,19,24,25]

It is interesting that the more recent suggestions for estimation of myocardial energy turnover from hemodynamic variables turn back to the additive concept of Frank's formula. Bretschneider developed an additive formula based on five components contributing to total energy turnover of the myocardium. These are E_0 for basal metabolism, E_1 and E_4 for electrophysiologic processes, and E_2 and E_3 for maintenance and development of tension.[8] This formula was shown to be valid in animal experiments for a broad range of hemodynamics and also proved to be a useful tool for the analysis of pathophysiologic settings.[8,25-27] A major drawback to clinical application of this formula is the requirement of a left ventricular tip manometer for measurement of dP/dt_{max}.

Rooke introduced an approach named the pressure work index (PWI), which is an additive combination of basal metabolism, RPP, and a term containing cardiac work.[5] In animal experiments performed by Rooke, it was found that this empiric formula was equivalent to

$$A = \underset{V_1}{\overset{V_2}{\int}} P\,dV - \underset{V_1}{\overset{V_2}{\int}} \psi(V)\,dV + \Sigma \frac{dm\,v_1^2}{2} - \Sigma \frac{dm\,v_2^2}{2} + R \pm Ai + W \quad \text{(Gl. 29)}$$

I II III IV V VI VII

FIG. 7. The original formula for the calculation of the total effort of the heart, developed by O. Frank in 1895. Since this was the first approach to describing all energy-consuming processes of the heart, it also must be considered the first approach to describing the determinants of myocardial oxygen demand. According to Frank, total energy turnover of the heart could be represented by a sum of several components: 1) pressure volume work done by the ventricles during systole; 2) potential energy in terms of pressure volume work, which is received by the ventricles during diastolic filling; 3) kinetic energy of the blood during systolic ejection phase; 4) kinetic energy of the blood during diastolic filling; 5) energy that is used to overcome frictional resistances of the myocardium; 6) changes of internal mechanical energy, which according to Frank is the motion of the smallest parts of the myocardial muscle (was he already thinking of small contractile elements?); and 7) heat due to biochemical conversion of energy. (Reproduced from Frank O: Die Grundform des arteriellen Pulses. Z Biol 36:483–526, 1895.)

Bretschneider's formula in predicting relative changes of myocardial oxygen consumption, and it was even superior for prediction of absolute values. Although the PWI of Rooke also requires invasive measurements for assessment of cardiac output, it is much more attractive for clinical application because, in contrast to Bretschneider's concept, a catheter tip manometer is not required. In most critically ill patients, the pulmonary artery catheter required for measurement of cardiac output is already available.

Underestimation of Myocardial Oxygen Consumption in Patients

It was observed in the current investigation that all commonly used hemodynamic indices of myocardial oxygen demand tend to underestimate $M\dot{V}_{O_2}$ in patients. In principle, it could be possible that this underestimation of $M\dot{V}_{O_2}$ results from methodologic reasons—in particular a systematic error in blood flow measurement. On the other hand, even if the argon wash-in technique is not necessarily the "gold standard" of myocardial blood flow measurement, it is currently the only method available in patients for measurement of blood flow per 100 g tissue. Indices of myocardial oxygen demand that are designed to calculate oxygen demand in terms of milliliters per minute per 100 g tissue therefore can be validated only by this method of direct oxygen consumption measurement.

However, it can be proved independently from blood flow measurements that constants for E_g derived from animal experiments are very unlikely to be valid for humans. If textbook data for blood pressure, dP/dt_{max}, heart rate, and ejection time for a resting patient in an awake state (left ventricular systolic pressure, 120 mmHg; dP/dt_{max}, 1,200 mmHg · s^{-1}; heart rate, 80 beats per min; t_e, 0.23 s) are used, an oxygen demand of 5.0 ml · min^{-1} · 100 g^{-1} would be calculated by the E_g formula. This is less than generally measured in humans during resting state conditions.[28] Considering thermodynamics, it is also theoretically too low because the resulting efficiency of myocardial performance would be unreasonably high: oxygen consumption at 5.0 ml · min^{-1} · 100 g^{-1} is equivalent to an energy turnover of 98 J · min^{-1} · 100 g^{-1}; external cardiac work calculated by the product of mean systolic blood pressure (112 mmHg)[29] and cardiac output (5.0 l · min^{-1}) is 50 J · min^{-1} · 100 g^{-1} (150 g of the left ventricular muscle weight; *i.e.*, free wall of the left ventricle plus septum is assumed)[30]; the resulting efficiency of myocardial energy conversion into external cardiac work would therefore amount to 51%. A hypothetical efficiency of 51% is a clear argument against the validity of E_g constants for human hearts. Efficiency of the oxidative phosphorylation is known to amount maximally to 70%.[31] Thus, only 67 J · min^{-1} · 100 g^{-1} of energy is available in the form of high-energy phosphates. Furthermore, energy is required for basal metabolism, electrophysiologic processes, and calcium movements across membranes.[7,8,13,31,32] Under resting state conditions, energy turnover for these processes is estimated to require more than 1 ml · min^{-1} · 100 g^{-1} O_2, [3,5,7,8] which is approximately 20 J · min^{-1} · 100 g^{-1}. The energy left for activity of the contractile elements therefore is in the range of 50 J · min^{-1} · 100 g^{-1} or even less. This already would be less than the resulting external cardiac work. However, several additional steps are necessary to convert the energy stored in high-energy phosphates into contractile element work and external pump work (*i.e.*, conversion of adenosine triphosphate energy into activities of actin–myosin filaments, transformation of this activity into wall tension, and conversion of wall tension into muscle shortening and ejection of blood). Because of the basic laws of thermodynamics, each of these steps cannot be performed with an efficiency of 100% and must be associated with loss of energy in the form of heat production. The remaining energy for the contractile element work therefore cannot account for the observed external work of 50 J · min^{-1} · 100 g^{-1}. Thus, it can be concluded independently from blood flow measurements that, during the resting state, myocardial oxygen demand of a human heart must be significantly greater than 5.0 ml · min^{-1} · 100 g^{-1}, which is calculated by E_g for these conditions. Therefore, the constants involved in the E_g formula must be inappropriate for human data.

Similar to the Bretschneider formula, PWI was found to underestimate $M\dot{V}_{O_2}$. This finding is consistent with the recent results of Hasenfuss *et al.*,[3] who also observed an underestimation of $M\dot{V}_O$ by PWI in 22 patients with dilated cardiomyopathy. In the current investigation, all of the patients had ischemic heart disease. Theoretically, it could be possible that ischemic heart disease and cardiomyopathy might have accounted for the fact that the observed myocardial oxygen consumption was greater than that estimated by PWI and E_g. Although all of the hearts studied in the current investigation showed normal contractility, this theoretic possibility cannot be excluded entirely from the data of the current investigation.

Clinical Application of PWI

Obviously, it is not possible to extrapolate from animal experiments to the human heart. RPP and TTI might be suitable for rough estimation of relative changes of myocardial oxygen demand in patients. The additive formula of Bretschneider is not directly applicable to patients because new constants must be developed. In principle, it could be possible to determine the necessary constants K_0 through K_4 retrospectively from the measured patient data by statistical methods, with a multilinear regression analysis. However, this kind of calculation is not well-suited for the current E_g data because the number of measurements and the limited variability of inotropic

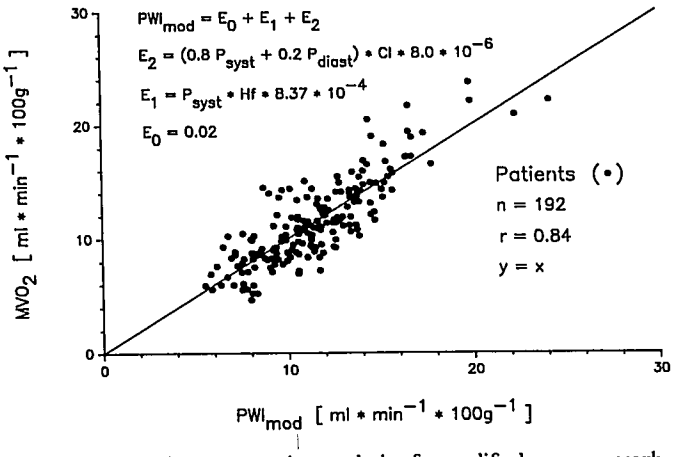

FIG. 8. Multilinear regression analysis of a modified pressure work index (PWI_{mod}) and myocardial oxygen uptake ($M\dot{V}O_2$) in patients. For clinical application, cardiac index (CI) was used instead of cardiac output, divided by body weight. New constants have been calculated by a multilinear regression fitting procedure. A significant improvement of the correlation coefficient can be achieved (see also fig. 4).

states in patients does not allow determination of the unknown constants with sufficient accuracy.

In contrast, more data are available for calculation of PWI, and only three instead of five constants must be determined. It is therefore possible to calculate new constants retrospectively for PWI by a multilinear regression. The results of such a fitting procedure are shown in figure 8. A linear regression coefficient of r = 0.84 and constants of 0.02 for K_0, $8.37 \cdot 10^{-4}$ for K_1, and $8.0 \cdot 10^{-6}$ for K_2 were found (fig. 8). The formula of the PWI was modified slightly for clinical use (PWI_{mod}). The term "$SV \cdot HR \cdot BW^{-1}$" of the original formula was replaced by cardiac index (CI [$l \cdot min^{-1} \cdot m^2$]), which is used more commonly in patients than cardiac output per kilogram of body weight. As a result of the fitting procedure, the mean difference between PWI_{mod} and $M\dot{V}O_2$ is zero and the standard deviation of the mean difference is ±1.98 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ (fig. 9); therefore, the limits of agreement are ±3.96. Although these limits of agreement seem to be large, it is in the same range as the limits of agreement for E_g and $M\dot{V}O_2$ under standardized experimental conditions in our laboratories (−4.69 to +3.91 $ml \cdot min^{-1} \cdot 100\ g^{-1}$; n = 119; r = 0.94, data not presented). Furthermore, it should be remembered that the sources for the scattering in the regression analysis of the data also result from inaccuracies of blood flow and oxygen content measurements. The true accuracy of PWI_{mod} therefore might be much better than was found in the current investigation.

With respect to the application of PWI_{mod} in anesthetized patients, it might be of interest to determine whether the relation between PWI_{mod} and $M\dot{V}O_2$ is also valid during anesthesia. The mean differences between PWI_{mod} and $M\dot{V}O_2$ and the corresponding standard deviations and 95% confidence limits for the mean differences therefore were also calculated for the awake state and for measurements obtained during anesthesia (table 2). No major systematic difference was found with respect to anesthetic state or surgical stimuli, which confirms the results of Rooke[6] obtained in dogs. Therefore, it seems that estimation of myocardial oxygen demand by PWI_{mod} is not affected by anesthesia.

According to the results of the current investigation, it seems questionable whether the more physiologic, but more invasive, approach of the E_g formula might be valuable for clinical investigations, even if appropriate constants for the human heart would be available. At least the limits of agreement for PWI_{mod} and $M\dot{V}O_2$ in patients are as good (or bad) as for E_g and $M\dot{V}O_2$ under experimental conditions. The main advantage of PWI_{mod} in comparison with E_g is the availability of the necessary data in many critically ill patients (*i.e.*, in all patients with cardiac output measurements). In all of these patients, estimation of $M\dot{V}O_2$ by PWI_{mod} could be more advisable than by RPP or TTI. Although not prospectively studied in this investigation, PWI_{mod} currently seems to be a promising approach for reliable calculation of myocardial oxygen demand in patients. However, it must be remembered that the results of the current study are confined to a selected group of patients with ischemic heart disease. The hemodynamic data obtained from these patients are limited compared with those from experimental animals, in which a wide range of data can be obtained. Therefore, it cannot be determined that these results also apply to other groups of patients (*i.e.*, patients with very high left ventricular pressures and heart rates, with failing hearts, hearts with dilatative cardiomyopathy, or small hearts [children]), until these patient groups have been evaluated prospectively.

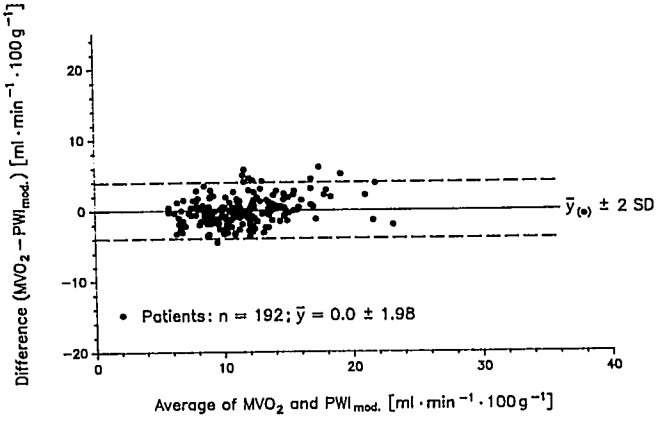

FIG. 9. Comparison of the modified pressure work index (PWI_{mod}) and myocardial oxygen uptake ($M\dot{V}O_2$) in patients, according to the method of Bland and Altman.[12] As a result of the multilinear fitting procedure, the mean difference between $M\dot{V}O_2$ and PWI_{mod} is 0. There is a significant improvement for the standard deviation of the mean difference and for the limits of agreement.

TABLE 2. Agreement between MV_{O_2} and Modified Pressure–Work Index

	n	mean (MV_{O_2} − PWI_{mod}) (ml·min^{-1}·100 g^{-1})	sd (MV_{O_2} − PWI_{mod}) (ml·min^{-1}·100 g^{-1})	95% LC (MV_{O_2} − PWI_{mod}) (ml·min^{-1}·100 g^{-1})
Awake	62	+0.23	±2.05	−0.29–+0.75
After induction	50	−0.61	±1.72	−0.46–−1.07
Sternotomy	50	+0.50	±2.12	−0.15–+1.14
End of surgery	30	−0.11	±1.65	−0.73–+0.51

PWI_{mod} = pressure work index; mean (MV_{O_2} − PWI_{mod}) = mean difference between MV_{O_2} and PWI_{mod}; sd (MV_{O_2} − PWI_{mod}) = standard deviation of mean difference between MV_{O_2} and PWI_{mod}; 95% LC (MV_{O_2} − PWI_{mod}) = 95% limits of confidence for the mean difference between MV_{O_2} and PWI_{mod}.

Statistical analysis for the agreement between MV_{O_2} and PWI_{mod} was performed using the method of Bland and Altman.[12] Introduction of anesthesia, sternotomy, and postbypass period did not influence the agreement between measured MV_{O_2} and PWI_{mod}.

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