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Contractility in Humans after Coronary Artery Surgery

Echocardiographic Assessment with Preload-adjusted Maximal Power

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Background: **Propofol's unique pharmacokinetic profile offers advantages for titration and rapid emergence in patients after coronary artery bypass graft (CABG) surgery, but concern for negative inotropic properties potentially limits its use in these patients. The current study analyzed the effect of various propofol plasma concentrations on left ventricular (LV) contractility by means of a single-beat contractile index based on LV maximal power (PWR_{max}).**

Methods: **The study was conducted in 30 patients after CABG surgery. Immediately after admission to the intensive care unit (ICU), four different plasma concentrations of propofol, 0.65, 1.30, 1.95, and 2.60 μg/ml, were established. At each concentration level, the cardiac and vascular effects of propofol were studied by combining echocardiographic data with invasively derived aortic root pressure. Preload was characterized by LV end-diastolic dimensions. Afterload was indicated in terms of indexed systemic vascular resistance (SVRI), LV end-systolic meridional wall stress (LV-ESWS), and arterial elastance (E_a). Quantification of effects on contractility was achieved by preload-adjusted PWR_{max}.**

Results: **Myocardial contractility did not change during a fourfold increase in propofol plasma concentration. Preload-adjusted PWR_{max} amounted to 3.90 ± 1.75 $W \cdot ml^{-2} \cdot 10^4$, 3.98 ± 1.69, 3.94 ± 1.70, and 3.88 ± 1.72, respectively (mean ± SD). With respect to ventricular loading conditions, propofol caused a significant reduction in both pre- and afterload.**

Conclusions: **The current results strongly suggest that propofol lacks direct cardiac depressant effects. Nevertheless, meaningful vascular actions of propofol could be demonstrated. Significant decreases in ventricular loading conditions accounted for a marked decrease in arterial blood pressure and supported the concept that propofol in clinically relevant concentration is a vasodilator. (Key words: Inotropic properties; myocardial function; propofol sedation; transesophageal echocardiography; ventricular power output.)**

PROPOFOL is commonly used to sedate patients after coronary artery bypass graft (CABG) surgery[1,2] but possesses cardiovascular depressant properties similar to or even greater than those of barbiturates.[3] Animal experiments and *in vitro* models suggest that adverse cardiovascular effects of propofol, including marked decreases in arterial blood pressure and cardiac output, are mainly related either to vasodilation,[4,5] to direct effects on myocardial contractility,[6–8] or both.[9,10] In particular, the possibility that propofol has a direct inhibitory effect on myocardial contractility remains controversial.[11–13] In humans limited information on direct cardiac effects of propofol provides conflicting results.[14–17] However, recent evidence suggests that propofol may exert more profound negative inotropic effects in the compromised myocardium than in normal hearts.[18,19] After cardiopulmonary bypass (CPB) and CABG surgery, left ventricular (LV) dysfunction consequent to impaired contractility is likely to occur and continues to be a common postoperative problem.[20,21] The administration of a negative inotropic drug in this setting may ultimately translate into further undesirable deterioration of LV function.

The susceptibility of traditional measures of LV performance to alterations in loading conditions contributes to the controversy about direct cardiac effects of propofol

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in humans. Conventional measures, such as ejection fraction (EF) and maximum rate of change of LV pressure (dP/dt_{max}), are influenced not only by inotropic properties of the LV but also by preload and afterload.[22] It is difficult to assess alterations in LV contractility in a clinical setting with afterload changing simultaneously, as it is observed during propofol infusion. To overcome these limitations and to clearly discriminate effects on load from effects on contractility, we applied a new approach to cardiac contractile assessment based on ventricular power (PWR). The ratio of maximal ventricular power corrected for preload (PWR_{max}/D^2) has the potential for noninvasive derivation and may provide excellent discrimination between vasodilatory drug effects and changes in inotropic properties.[23–25]

Accordingly, this study was designed to evaluate mechanisms responsible for the cardiovascular depressive actions of propofol in mechanically ventilated patients after CABG surgery, using the concept of PWR_{max}/D^2 to focus particularly on the direct effects of propofol on LV contractility.

Materials and Methods

Study Population

With approval by the Ethics Committee of the University Hospital of Gent, Belgium, and with patients' consent, 30 consecutive American Society of Anesthesiologists physical status III or IV postoperative elective CABG patients were included in the study. Exclusion criteria comprised of (1) any esophageal or gastric pathology diagnosed as contraindication to transesophageal echocardiography (TEE), (2) hemodynamic instability at admission to the intensive care unit (ICU), (3) administration of inotropic agents, (4) intraaortic balloon pump therapy, (5) preexisting segmental wall motion abnormalities at the midpapillary short-axis level of the LV, (6) concomitant valvular diseases, (7) supraventricular or ventricular rhythm disturbances, and (8) pronounced hypovolemia diagnosed on hemodynamic or echocardiographic features. Hemodynamic stability was defined as a systolic arterial blood pressure (P_{syst}) of more than 90 mmHg for 10 min without therapeutic interventions.

Preoperatively all patients were taking nitrates. All but four patients were taking β-adrenoreceptor blocking or calcium-channel blocking drugs, or both. Routine oral medication was continued until the morning of surgery.

Anesthetic Management and Surgery

On arrival in the operating room, leads II and V5 electrocardiographic (ECG) monitoring was performed. A central venous catheter was inserted *via* an internal jugular vein. A brachial artery was cannulated to insert a catheter (Laboratoire Plastimed, Saint-Leu-La-Forêt, France), which was advanced into the LV. Afterward, it was pulled back until the LV pressure trace disappeared. This system is typical for a fluid-filled catheter system in clinical use.[26] It has been tested and qualified with respect to its resonant frequency (13.7 Hz) and damping ratio (0.62).

Anesthesia comprised of bolus injections of sufentanil plus midazolam, likewise for induction and maintenance (5–10 μg/kg and 0.2–0.5 mg/kg, respectively), and pancuronium bromide for muscle relaxation. During maintenance isoflurane was added as needed for intraoperative control of blood pressure.

Experimental Protocol

Postoperatively in the ICU, patients were mechanically ventilated with oxygen in air ($F_{I_{O_2}} = 0.5$). Nitroglycerin was started during separation from CPB and maintained ($0.20 \pm 0.1\ \mu g \cdot kg \cdot min^{-1}$). An infusion of glucose 5% ($5–10\ ml \cdot kg^{-1} \cdot h^{-1}$) was initiated for compensation of urinary losses of fluid (411 ± 228 ml in the course of the study). As changes in heart rate are likely to affect the force of ventricular contraction, atrial pacing *via* an epicardial pacemaker wire was instituted at a fixed rate (92 ± 5 beats/min) and continued throughout the study period. Having achieved hemodynamic stability, the experimental protocol was initiated, and no further changes in the therapeutic regimen were allowed. The study started approximately 2 h (2:06 ± 0:30 h) after release of the aortic cross-clamp. No anesthetic agents were administered between the end of surgery and the start of the experimental protocol. The complete study period lasted 1:05 ± 0:12 h.

The hemodynamic effects of propofol sedation were evaluated at four different calculated plasma concentrations (0.65, 1.30, 1.95, and 2.60 μg/ml), which were selected according to previous studies in patients after cardiac surgery.[1,2] Propofol (Zeneca, Destelbergen, Belgium) was given *via* the central venous catheter with an infusion pump ("Anaesthesia pump 3500," Graseby Medical LTD, Watford, UK) driven by a portable Compaq 486 computer (Houston, TX). Patients were allocated randomly to receive propofol infusions to reach certain plasma concentrations either in a chronologically ascending or descending order. To overcome the problem of long equilibration times for attaining steady-state concentrations, a target-controlled infusion (TCI) technique was applied ("Stanpump," Stanford University, Anesthe-

siology Service, Palo Alto, CA). The program "Stanpump" is based on a three-compartment pharmacokinetic model[27] and has been proven to be accurate in the cardiac surgical population.[28] Hemodynamic and echocardiographic measures were taken when complete intercompartmental steady-state of propofol at the required four plasma concentrations was attained. The plasma concentrations were estimated by "Stanpump" deduced from population-based averages and indicated on the computer display.

None of the patients reacted to insertion of the TEE probe with an increase in P_{syst} by more than 5%. Nevertheless, patients were left without stimulation for 10 min before data collection was commenced and for an additional 3 min after each manipulation of the TEE probe to prevent hemodynamic reactions. Multiplane TEE examination was performed with a Hewlett-Packard 5-MHz, 64-element multiplane probe and a Hewlett-Packard Sonos 2500 (Hewlett-Packard Co., Andover, MA). TEE images were acquired along with a lead II of the ECG and stored on videotape. All echocardiographic data were collected with ventilation held at end-expiration and with the patient in the supine position. Echocardiographic analysis was performed off-line with the same ultrasonographic system.

A standard series of TEE recordings were repeated under stable hemodynamics whenever one of the four predetermined plasma concentrations of propofol was reached. Data were collected during the following four transducer positions within 60–90 s (fig. 1):

1. Transgastric TEE imaging plane visualizing the long-axis of the heart from an apical approach to register pulsed-wave Doppler flow pattern within the LV outflow tract (LVOT) just beneath or at the level of the aortic valve (fig. 1A, 1B).
2. Transgastric midpapillary short-axis view of the LV to obtain endo- and epicardial LV dimensions at end-systole and end-diastole by two-dimensional (2D) echocardiography.
3. Midesophageal two-chamber view of the LV in a longitudinal imaging plane allowing for the derivation of LV end-systolic and end-diastolic volumes by 2D echocardiography (fig. 1C).
4. Basal short-axis view with the transducer rotated to around 30° to depict the aortic valve orifice (fig. 1D).

At 1. Recordings of 5–10 cardiac cycles were made at a sweep speed of 100 mm/s. For off-line analysis of Doppler registrations, three consecutive high-quality Doppler spectra were analyzed, and the average of each of the following parameters was computed: peak velocity, time velocity integral (TVI, *e.g.*, the integration of instantaneous blood flow velocities with respect to time during one cardiac cycle), left ventricular ejection time (LVET), and the time delay between onset of aortic flow and peak velocity. Furthermore, readings of flow velocities were obtained at 5-ms intervals starting at the top of the flow velocity waveform. All velocity spectra were traced manually by using the leading edge (highest velocity) contours.

At 2. Two-dimensional echocardiographic images with the largest cross-sectional area and overall circular geometry were recorded. Echocardiograms were analyzed as follows. End-diastolic and end-systolic contours of both endocardial and epicardial LV contours were tracked corresponding to the leading-edge to leading-edge method with the papillary muscles included. End-diastole was identified by the peak of the R-wave. End-systole was defined as the smallest LV silhouette. Three consecutive heart cycles were analyzed and averaged with respect to LV end-systolic (LV-ESD) and end-diastolic internal diameter (LV-EDD) and circumference, end-systolic (LV-ESA) and end-diastolic cross-sectional area (LV-EDA), end-systolic epicardial area, and end-systolic septal wall thickness (ESWT).

At 3. End-systolic and end-diastolic borders of the LV were outlined, and ventricular volumes were calculated using the software routines of the ultrasonograph (Simpson's rule).

At 4. For evaluation a stop frame was chosen, in which aortic valve area (AVA) during systole appeared precisely as an equilateral triangle. The length of each cusp was measured, and the average value was taken for substitution in the following formula: $AVA = \cos 30° \cdot L^2 = 0.433 \cdot L^2$ (cm^2), where L is the average length of the three sides of the triangle.[29]

Doppler echocardiographic flowmetry and central arterial pressure were recorded simultaneously. Waveforms were displayed on a monitor and digitally processed *via* an analog-to-digital converter with a 12-bit resolution (DI-200 PGH/PGL; Dataq Instruments, Akron, OH). For storage and calculation pressure data were recorded together with a limb lead of the ECG at a sampling rate of 200 Hz/channel on a personal computer. Video recordings of Doppler velocity spectra and digital recordings of central arterial pressure waveforms were synchronized. Event markers allowed for the recognition of identical heart cycles on the computer device and on the video tape, facilitating analysis of the data on a beat-to-beat basis. Analysis was performed

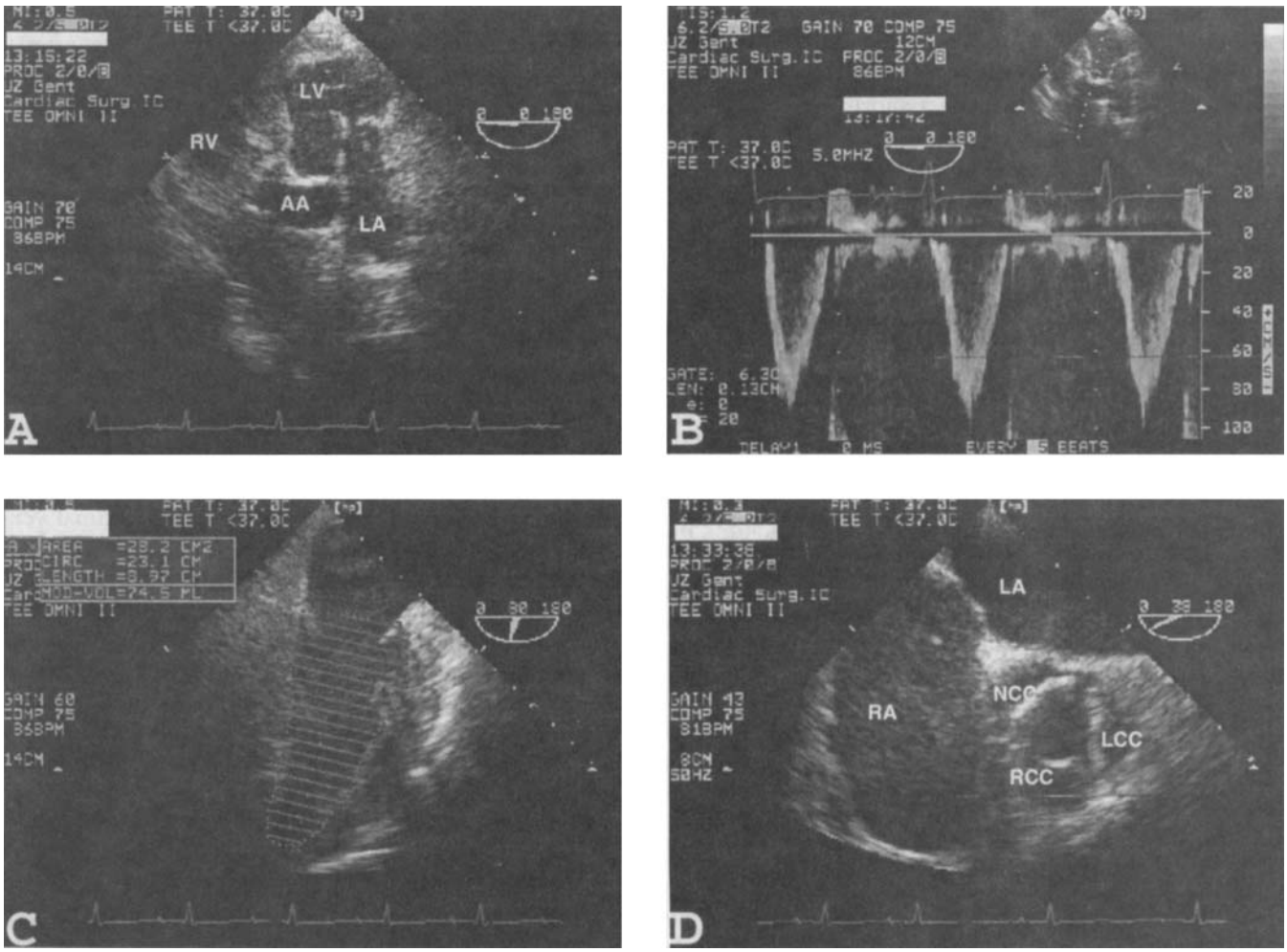

Fig. 1. TEE registrations of a representative patient. (*A*) Modified transgastric long-axis view. AA = ascending aorta; LA = left atrium; LV = left ventricle; RV = right ventricle. (*B*) Pulsed-wave Doppler echocardiography at the level of the aortic valve. Blood flow velocity is given in cm/s. (*C*) Two-chamber view of the left ventricle in a longitudinal imaging plane. Semi-automated calculation of LV volume according to the Simpson's rule is demonstrated. (*D*) Short-axis image of the aortic valve. Aortic opening appears as an equilateral triangle. LCC, RCC, NCC = left-, right-, and non-coronary cusp.

using commercially available data acquisition software (Dataq Instruments). Pressure waveforms were examined for systolic (P_{syst}), end-systolic (P_{es}), diastolic (P_{diast}), and mean (P_{mean}) arterial pressure. Moreover, on the ascending part of the waveform the point was identified where peak flow velocity occurred.

Assessment of Preload

The relevant indication of LV preload is end-diastolic fiber length, which reflects the maximal resting length of the sarcomere. In the intact heart, LV end-diastolic volume (LV-EDV) is generally accepted as a reliable surrogate measure of true ventricular preload because it approximates muscle fiber length most closely. Different geometric and mathematic models for the estimation of LV volumes from 2D echocardiographic images have been used. The most accurate approach is based on the angiographically validated Simpson's rule.[30] Simpson's rule divides the ventricle into 20 individual slices of known thickness. The sum of the cylindric slices represents total LV volume. The Simpson's rule is integrated in the computer software of the Hewlett Packard Sonos 2500 ultrasonograph system and was applied in this investigation to compute LV-EDV and LV end-systolic volume (LV-ESV) from a longitudinal two-chamber view as demonstrated in figure 1C.

Transesophageal echocardiography has also been used to measure LV-EDA at a midpapillary short-axis plane as

a reasonable approximation of LV volumes.[31] With reservation these considerations are even valid for a single ventricular internal diameter. In this study LV-EDA and LV-EDD were determined from a short-axis view as described previously.

End-diastolic ventricular dimensions were related to end-systolic dimensions to derive the respective percent fiber shortening parameter according to the formula:

$$\text{Percent fiber shortening} = \frac{(\text{LV-EDDi} - \text{LV-ESDi})}{\text{LV-ESDi}} \cdot 100\ (\%)$$

where LV-EDDi = left ventricular end-diastolic dimension and LV-ESDi = left ventricular end-systolic dimension. Percent fiber shortening is a global descriptor of pump performance that reflects the interaction between ventricular loading conditions and contractile state.[32] By substituting the appropriate three-dimensional (3D), 2D, and one-dimensional (1D) variables in the above formula, ejection fraction (EF), fractional area change (FAC), and fractional shortening (FS) were calculated.

Assessment of Afterload

End-systolic meridional wall stress (LV-ESWS) as an indication of LV afterload can be derived from the basic Laplace relationship by combining ventricular dimensions with ventricular wall thickness and systolic arterial pressure according to a catheterization-validated formula presented by Reichek *et al.*[33]:

$$\text{LV-ESWS} = \frac{0.334 \cdot P_{syst} \cdot \text{LV-ESD}}{\text{ESWT}\left(1 + \frac{\text{ESWT}}{\text{LV-ESD}}\right)} \times (10^3 \cdot \text{dyne} \cdot \text{cm}^{-2})$$

where P_{syst} = systolic arterial blood pressure, LV-ESD = left ventricular end-systolic internal diameter, and ESWT = end-systolic septal wall thickness. Left ventricular end-systolic minor-axis dimension and wall-thickness measurements were obtained from 2D echocardiographic recordings (midpapillary short-axis view). Wall thickness was measured at the septal wall of the LV. P_{syst} was determined on the basis of digitally stored pressure waveforms of the same cardiac cycles. Values from three consecutive beats were averaged.

Clinically, it is common practice to use indexed systemic vascular resistance (SVRI) as a description of afterload, although this approach fails to account for the effect that ventricular geometry has on the load imposed on the myocardium. Compared with SVRI, which is an indication of steady-state resistance, effective arterial elastance (E_a) is a more complete index of arterial load. Kelly *et al.* evidenced that this simple parameter shows nearly perfect agreement with invasively derived vascular impedance spectra, qualifying E_a for expressing the major vascular loading conditions.[34] E_a is related to the formula:

$$E_a = P_{es} \cdot SV^{-1}\ (\text{mmHg} \cdot \text{ml}^{-1})$$

where P_{es} = end-systolic arterial pressure, and SV = stroke volume. P_{es} was the pressure at the incisura of the digitized waveform.

Assessment of Contractility

Direct assessment of inotropic state of the LV is possible by measuring preload-adjusted maximal ventricular power (PWR_{max}/D^2).[23] PWR, the rate at which the ventricle performs external work, can be calculated from simultaneous records of ventricular pressure and rate of volume change throughout the ejection period. Mathematically speaking, PWR equals the product of pressure and volume change at every instant.[35] In the absence of mitral regurgitation, the rate of ventricular volume change during systole equals aortic volumetric flow, and therefore PWR can be expressed as follows:

$$\text{PWR}\ (t) = P_{LV}(t) \cdot F_{Ao}(t)$$

where $P_{LV}(t)$ = instantaneous LV pressure, and $F_{Ao}(t)$ = instantaneous aortic flow. The product shows its maximum value soon after the onset of ejection when central arterial and ventricular pressures are similar. This fact allows for accurate derivation of PWR_{max} from the pressure-flow product in the outflow artery, and invasive instrumentation of the LV can be avoided (in the absence of aortic valve dysfunction).[36] Hence, PWR_{max} is calculated as:

$$PWR_{max} = \{P_{Ao}(t) \cdot F_{Ao}(t)\}_{max}$$

where P_{Ao} = instantaneous aortic pressure, and F_{Ao} = instantaneous aortic flow. Because PWD echocardiography offers reliable estimates of volumetric aortic flow at the patients' bedside,[37] PWR_{max} is readily accessible in the perioperative setting by combining Doppler echocardiographic and pressure data. In the current investigation, central aortic pressure was registered beneath the level of the aortic valve, and the adapted following formula was used to derive PWR_{max}:

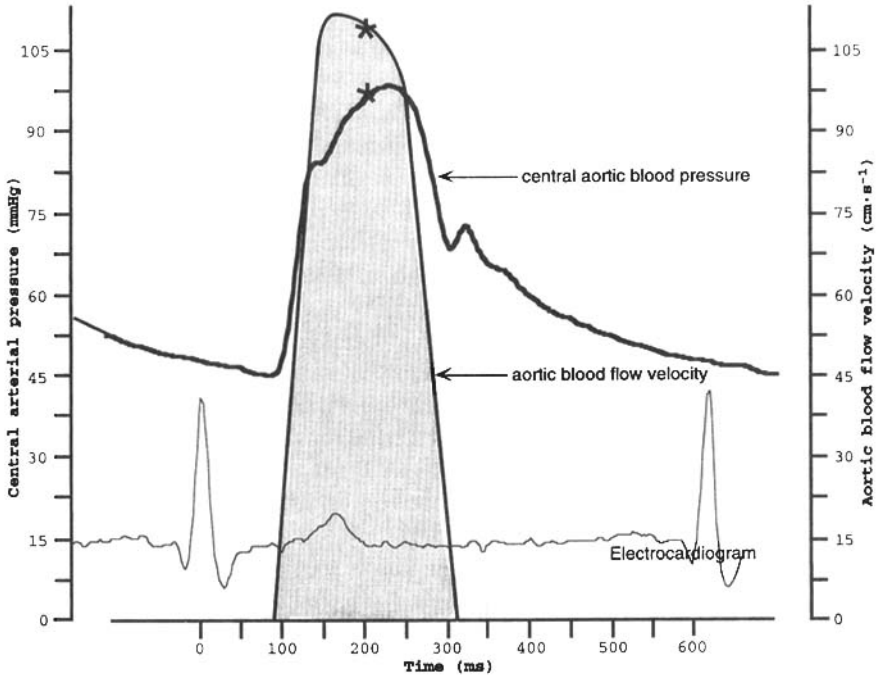

Fig. 2. Schematic diagram depicting electrocardiogram, central aortic pressure, and aortic blood flow velocity. Original tracings of a representative patient are plotted together. For a more concise illustration, flow waveform is flipped around its horizontal axis. *Indicates the maximal pressure–flow velocity product. Multiplication of the product by aortic valve orifice area results in maximal power.

$$PWR_{max} = \{P_{Ao}(t) \cdot V_{Ao}(t)\}_{max} \cdot AVA \cdot 1.333 \cdot 10^{-4}$$

where V_{Ao} = instantaneous aortic blood flow velocity, AVA = time-averaged aortic valve area, and $1.333/10^4$ is a factor to convert PWR_{max} units to watts (mmHg · ml · $s^{-1} \cdot 10^{-4}$).

PWR_{max} was calculated as schematically represented in figure 2. First identical cardiac cycles were detected on the different storage media. In a second step the velocity profiles were examined with respect to the time interval from the onset of flow to the occurrence of maximum flow velocity. This time interval was then allocated to the corresponding digitized aortic pressure waveforms. Starting at the time when peak flow velocity occurred, velocity and pressure data were read every 5 ms until the cessation of blood flow. The velocity signals were converted into volumetric flow by multiplication with the cross-sectional area of the aortic valve. Finally, matching flow-pressure pairs were multiplied, and the maximum product was designated for PWR_{max}.

Although displaying marked stability in the face of changes in afterload, PWR_{max} is sensitive to preloading conditions. To generate an index that exclusively quantifies contractile properties of the LV, normalization of PWR_{max} to the square of LV-EDV,[23,25,38] or a regional approximation like LV-EDA, and LV-EDD[24] was found to be appropriate. The normalized index is called PWR_{max}/D^2, where the abbreviation "D" substitutes any of the possible preload parameters.

Control Group

An independent control group of 15 American Society of Anesthesiologists physical status III and IV patients, who did not meet the exclusion criteria, was added to establish the impact of the lowest dose of propofol *versus* baseline. This group did not differ from the original study group with respect to biometrical data, risk stratification, course of anesthesia, and surgical management. In contrast to the original group, the patients of the control group were subjected to a different experimental protocol:

1. The TEE probe was already inserted after induction of anesthesia; and
2. Immediately after arrival on the ICU echocardiographic and pressure measurements were taken without running propofol (baseline) and at a propofol concentration of 0.65 μg/ml.

Statistical Analysis

Statistical evaluation was performed using a personal computer-based package (SPSS Inc., Chicago, IL). All data are given as mean ± SD. All paired hemodynamic data in the study group were compared using repeated measures

Table 1. Hemodynamic Variables at Four Different Plasma Concentrations of Propofol

Variable	0.65 μg · ml^{-1} (mean ± SD)	1.30 μg · ml^{-1} (mean ± SD)	1.95 μg · ml^{-1} (mean ± SD)	2.60 μg · ml^{-1} (mean ± SD)	F	*P*	Significant Contrasts	
							Difference*	Polynomial†
P_{syst}	114 ± 18	101 ± 12	96 ± 10	93 ± 9	41.10	0.000	a; b; c	1; 2; 3
P_{diast}	66 ± 9	60 ± 8	57 ± 7	55 ± 6	46.52	0.000	a; b; c	1; 2
P_{mean}	82 ± 11	74 ± 8	70 ± 7	68 ± 6	45.50	0.000	a; b; c	1; 2
P_{es}	80 ± 12	71 ± 7	67 ± 7	65 ± 6	43.75	0.000	a; b; c	1; 2; 3
CVP	9 ± 3	9 ± 2	9 ± 2	9 ± 2	3.13	0.030	a	3
LV-EDD	4.7 ± 0.7	4.6 ± 0.7	4.5 ± 0.8	4.4 ± 0.8	8.82	0.000	b; c	1
LV-ESD	3.2 ± 0.9	3.0 ± 0.8	2.9 ± 0.9	2.8 ± 0.9	3.36	0.022	c	1
FS	34.1 ± 12.7	35.1 ± 13.4	35.4 ± 16.6	37.0 ± 16.7	0.35	0.791		
LV-EDA	16.4 ± 4.7	16.0 ± 5.0	15.7 ± 5.6	15.2 ± 5.2	2.20	0.093		
LV-ESA	9.4 ± 4.2	8.6 ± 4.0	8.3 ± 4.4	7.5 ± 3.8	15.81	0.000	a; b; c	1
FAC	43.7 ± 12.4	46.8 ± 13.2	49.3 ± 9.8	52.3 ± 12.2	6.86	0.000	b; c	1
LV-EDV	122 ± 33	115 ± 31	112 ± 29	111 ± 31	10.59	0.000	a; b; c	1; 2
LV-ESV	57 ± 24	51 ± 25	48 ± 21	46 ± 20	14.49	0.000	a; b; c	1; 2
EF	55 ± 11	57 ± 12	58 ± 12	59 ± 10	8.51	0.000	a; b; c	1
SVRI	1,951 ± 600	1,782 ± 493	1,677 ± 475	1,612 ± 484	26.91	0.000	a; b; c	1; 2
E_a	1.34 ± 0.53	1.21 ± 0.44	1.14 ± 0.39	1.09 ± 0.41	25.96	0.000	a; b; c	1; 2
LV-ESWS	58 ± 29	48 ± 22	43 ± 22	39 ± 18	10.31	0.000	a; b; c	1
Aortic flow	353 ± 90	352 ± 92	353 ± 87	358 ± 93	0.35	0.791		
SVI	34 ± 8.9	34 ± 9.0	34 ± 9.4	34 ± 9.5	0.46	0.713		
CI	3,144 ± 752	3,088 ± 754	3,104 ± 785	3,135 ± 808	0.46	0.713		
PWR_{max}	5.05 ± 1.53	4.64 ± 1.41	4.36 ± 1.19	4.22 ± 1.23	18.57	0.000	a; b; c	1
PWR_{max}/EDD^2	2.32 ± 0.86	2.32 ± 1.02	2.36 ± 0.94	2.37 ± 1.01	0.10	0.962		
PWR_{max}/EDA^2	2.16 ± 1.03	2.25 ± 1.04	2.35 ± 1.08	2.27 ± 1.05	0.39	0.758		
PWR_{max}/EDV^2	3.90 ± 1.75	3.98 ± 1.69	3.94 ± 1.70	3.88 ± 1.72	0.21	0.886		

P_{syst} = systolic arterial blood pressure; P_{diast} = diastolic arterial blood pressure; P_{mean} = mean arterial blood pressure; P_{es} = end-systolic arterial blood pressure; CVP = central venous pressure; LV-EDD = left ventricular end-diastolic internal diameter; LV-ESD = left ventricular end-systolic internal diameter; FS = fractional shortening; LV-EDA = left ventricular end-diastolic cross-sectional area; LV-ESA = left ventricular end-systolic cross-sectional area; FAC = fractional area change; LV-EDV = left ventricular end-diastolic volume; LV-ESV = left ventricular end-systolic volume; EF = ejection fraction; SVRI = indexed systemic vascular resistance; E_a = effective arterial elastance; LV-ESWS = left ventricular end-systolic meridional wall stress; SVI = stroke volume index; CI = cardiac index; PWR_{max} = maximal power.

* The letters a, b, and c indicate significant differences between plasma concentrations of propofol: a = 0.65–1.3 μg/ml; b = 1.3–1.95 μg/ml; c = 1.95–2.60 μg/ml.

† The numbers 1, 2, and 3 indicate statistically significant differences obtained with ANOVA tests with polynomial contrasts (see text for details).

analysis of variance (ANOVA) with *post hoc* polynomial contrasts and comparison of successive differences. In addition, the covariation between power indexes and stroke volume index (SVI), or LV-EDV, was assessed by regression statistics with subsequent curve estimation using SVI, or LV-EDV, as dependent variables. Paired *t* test was applied to compare the results within the control group. Independent-samples *t* test was used to evaluate differences between identical propofol plasma concentrations of the control group and the study group. Statistical significance was accepted at $P < 0.05$.

Results

No significant difference in any demographic or hemodynamic variable was documented between patients treated with the lowest propofol concentration first or with the highest concentration first. Therefore data from all 30 patients were pooled for further analysis.

The study population consisted of 23 male and 7 female patients (age, 62.9 ± 11.7 yr). EF was 62 ± 13%; aortic cross-clamp time was 38.2 ± 13.5 min. The study period began 2:06 ± 0:30 h after release of the aortic cross-clamp. Maintenance rates of propofol at equilibrium for the different plasma concentrations were 26 ± 7 μg · kg · min^{-1}, 59 ± 9, 93 ± 5, and 130 ± 9, respectively. None of the patients was lost as a result of an inability to obtain the appropriate echocardiographic registrations.

Hemodynamic and echocardiographic variables related to four different plasma concentrations of propofol are listed in table 1. Propofol caused significant and dose-related decreases in central aortic pressures (P_{syst}, P_{diast}, P_{mean}, and P_{es}). In figure 3 the changes in P_{syst} and peak aortic volumetric flow are plotted as a function of the propofol plasma concentration. Although there was a significant decrease in P_{syst} ($P = 0.000$), peak flow remained stable. The stability noted for peak flow was also observed for SVI. SVI was 34 ± 8.9 ml · beats^{-1} · m^2,

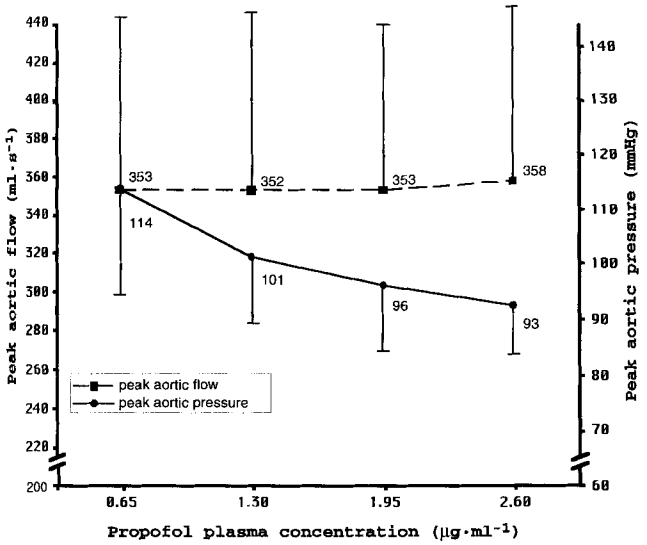

Fig. 3. Peak aortic pressure and flow at different propofol plasma concentrations. Peak flow displays remarkable stability, whereas pressure drops significantly. Means of flow and pressure are given also as numericals beside the corresponding data point. *P* values in the ANOVA are 0.791 and 0.000, respectively.

34 ± 9.0, 34 ± 9.4, 34 ± 9.5 (P = 0.713) for increasing propofol concentrations.

The trend observed for peak flow and P_{syst} was also valid for the distinct flows and pressures at the moment when PWR_{max} occurred. Hence the decrease in aortic pressure fully accounted for the detected decrease in maximal power output of the LV, which adds up to 16%. As the subjects were unselected with regard to their preoperative LV function, PWR_{max} data scattered over a broad range (2.26–8.80 W). Mean ± SD of PWR_{max} at different propofol concentrations are shown in figure 8.

The decline in PWR_{max} with increasing propofol concentrations was found to be highly significant (P = 0.000). Both PWR_{max} and SVI varied in direct relationship to preload by the Frank-Starling mechanism.[32] Strong preload dependence explains the correlation observed between these different indications of overall LV performance (fig. 4). For illustrative purposes, data of all patients on four occasions of data acquisition are plotted together in this graph. In contrast, when substituting PWR_{max} with load-independent PWR_{max}/EDV^2 no interdependence with SVI was observed (fig. 5).

Figure 6 outlines the variations in preload during graded intravenous infusions of propofol. LV end-diastolic chamber dimensions decreased by 7.9%, 7.4%, and 8.2% for LV-EDD, LV-EDA, and LV-EDV, respectively. Although preload reduction was small in quantity, it was roughly the same for regional and global measures, and changes could uniformly be proven in every patient. Similarly propofol led to a decrease in end-systolic ventricular dimensions. The overall effect of changes in end-diastolic and end-systolic ventricular dimensions resulted in a statistically significant increase in percent fiber shortening for ascending plasma levels of propofol. FAC increased from 44% to 52% (P = 0.000), and EF increased from 54% to 59% (P = 0.000).

The effects of propofol on LV afterload were quantified with LV-ESWS, SVRI, and E_a. The results are summarized in figure 7. A fourfold increase in propofol plasma concentration was associated with a 17.4% reduction in SVRI and an 18.7% reduction in E_a. LV-ESWS, an index of afterload that incorporates LV short-axis dimensions and wall thickness, decreased more prominently by 32.5%. All changes were dose-related and significant.

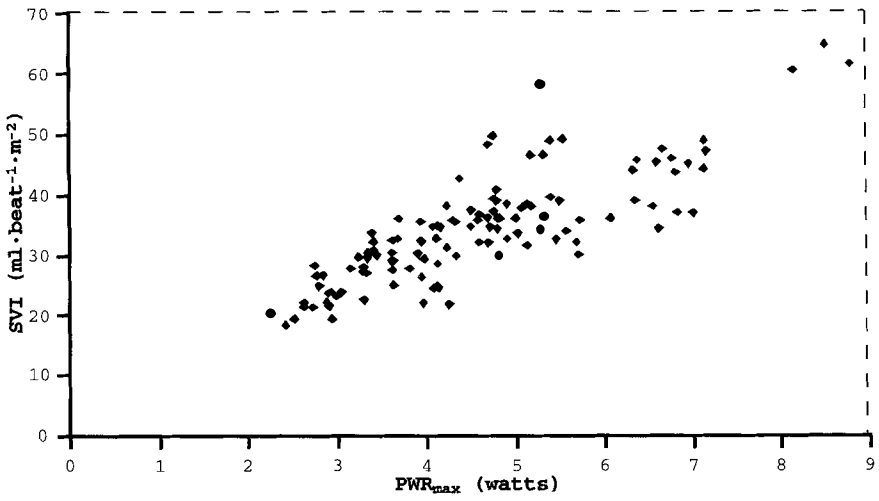

Fig. 4. Regression analysis: Stroke volume index (SVI) *versus* maximal ventricular power (PWR_{max}). For illustrative purposes, data of all patients on four occasions of data acquisition are plotted together in one graph. Pearson correlation coefficients (r) for the distinct propofol plasma concentrations are: $r_{0.65}$ = 0.86, $r_{1.30}$ = 0.86, $r_{1.95}$ = 0.80, and $r_{2.60}$ = 0.83.

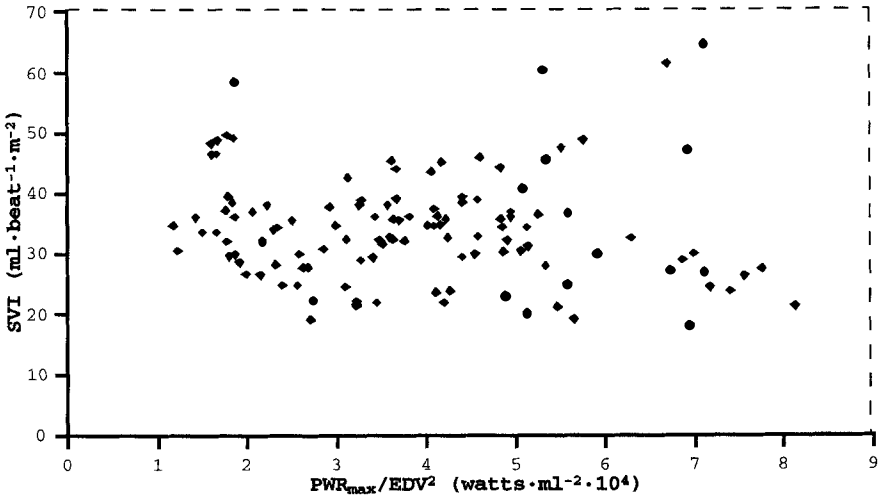

Fig. 5. Scatterplot of the relationship between stroke volume index (SVI) as dependent variable and maximal ventricular power divided by the square of end-diastolic volume (PWR_{max}/EDV^2) as independent variable. For illustrative purposes, data of all patients on four occasions of data acquisition are plotted together in one graph. Pearson correlation coefficients (r) for the distinct propofol plasma concentrations are: $r_{0.65} = 0.00$, $r_{1.30} = 0.10$, $r_{1.95} = 0.09$, and $r_{2.60} = 0.09$

Figure 8 pinpoints the behavior of PWR_{max} as opposed to PWR_{max}-indexes, which are corrected for preload volume, or dimension. PWR_{max}/EDD^2, PWR_{max}/EDA^2, PWR_{max}/EDV^2 did not vary, emphasizing that LV contractility remained unchanged in the range of propofol plasma concentrations under experimentation.

Data of the control group are presented in table 2. There were neither any significant differences in PWR_{max}, PWR_{max}/EDV^2, LV-ESWS, and LV-EDV between baseline and the lowest plasma concentration of propofol in the control group, nor were there any differences between the lowest plasma concentrations of propofol between the control group and the study group.

Discussion

The main finding of this study was: Propofol did not depress myocardial contractility in humans after CABG

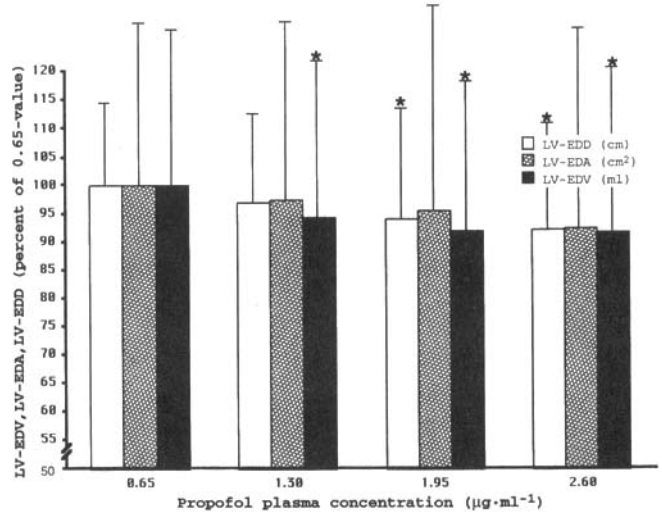

Fig. 6. Estimates of left ventricular preload. LV-EDV = left ventricular end-diastolic volume, LV-EDA = left ventricular end-diastolic area, LV-EDD = left ventricular end-diastolic internal diameter. Data are represented as a percentage of the lowest propofol plasma concentration. LV-EDV and LV-EDD change significantly during increases in propofol plasma concentration, and there is a similar trend for LV-EDA, although this does not reach statistical significance (see table 1). Significance for successive differences within each variable is indicated by an asterisk.

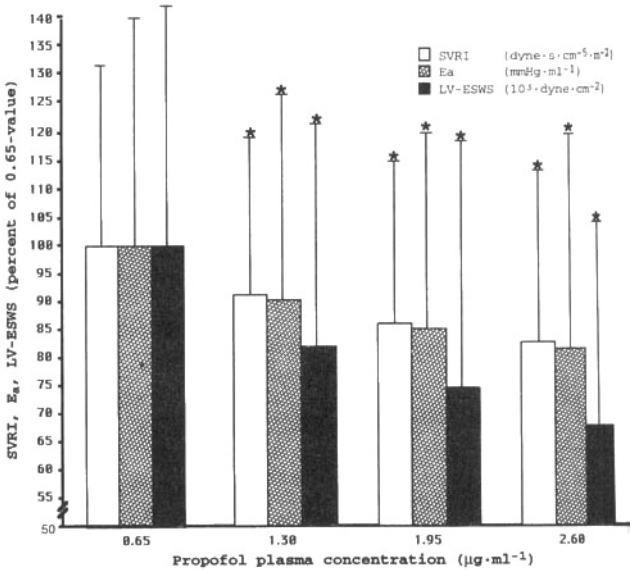

Fig. 7. Estimates of left ventricular afterload. SVRI = systemic vascular resistance index, E_a = effective arterial elastance, LV-ESWS = left ventricular end-systolic wall stress. Data are presented as a percentage of the lowest propofol plasma concentration. All paired values change significantly during increases in propofol (ANOVA). Significance for successive differences within each variable is indicated by an asterisk.

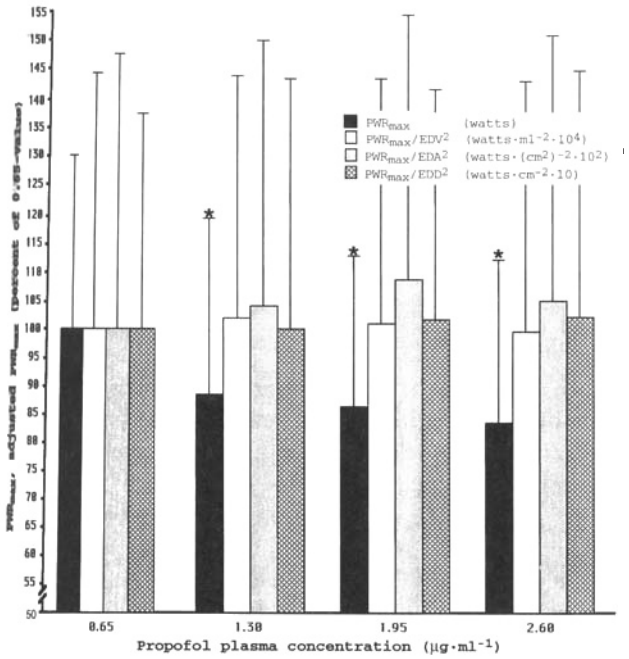

Fig. 8. Responses of maximal power (PWR_{max}) and preload-adjusted maximal power indexes (PWR_{max}/EDD^2, PWR_{max}/EDA^2, PWR_{max}/EDV^2) on increases in propofol plasma concentration. Data are presented as a percentage of the lowest propofol plasma concentration. Only changes in PWR_{max} display statistical significance (ANOVA). Significance for successive differences within each variable is indicated by an asterisk.

surgery in plasma concentrations up to 2.60 μg/ml. The hemodynamic actions of propofol could be explained by decreases in pre- and afterload.

Our experimental approach enabled distinction between drug effects on myocardial contractility and ventricular loadings. Assessment of contractility was based on an index derived from PWR. For the intact ventricle PWR represents the analog to the area under a force-velocity curve for isolated muscle.[39] The close relationship to the force-velocity curve strongly suggests that PWR, and in particular PWR_{max}, reflects contractile strength of the ventricle. This potential of PWR indexes was recently demonstrated in animal experiments and in human studies.[23-25,40] These investigations validated the anticipated afterload independency of PWR_{max} as well as its marked dependence on preload. The observed relative insensitivity of PWR_{max} to LV afterload is attributable to offsetting effects of changes in arterial load on flow and pressure. On the other hand, PWR_{max} highly depends on preload volume. This follows from the fact that peak flow and ejection pressure vary directly with preload by the Frank-Starling mechanism. As predicted by theoretical analysis, the dependence on preload volume was found to be parabolic in nature and to be virtually abolished by dividing PWR_{max} by the square of LV-EDV[23] or by a regional approximation of LV-EDV.[24,40] Consequently, in this study the concept of PWR_{max}/D^2 was used to gather a sensitive and specific index of contractile function, which is reasonably independent from ventricular loadings.

Originally, aortic flow data and LV volumes were estimated by radionuclide ventriculography.[25,38] Kelly *et al.*[36] were in the position to verify that LV power output can also be accurately and repeatedly assessed by PWD echocardiographic measurement of ascending aortic velocity profiles. As TEE is already well established as an invaluable noninvasive tool for monitoring cardiovascular function in the critically ill, Kelly's experimental procedure was adopted in the present study. PWR_{max}/EDV^2 values in this investigation were remarkably stable for different propofol plasma concentrations: $3.90 \pm 1.75\ W \cdot ml^{-2} \cdot 10^4$, 3.98 ± 1.69, 3.94 ± 1.70, and 3.88 ± 1.72, respectively. Furthermore, our data suggest that LV-EDV could easily be substituted by regional approximations like LV-EDA or LV-EDD to correct PWR_{max} for preload dependence. This finding supports others' results.[24,40]

No PWR_{max}/EDV^2 estimates for patients after CABG surgery, or, more generally, for ICU patients have been published so far. In a group of patients suffering from dilated cardiomyopathy, Sharir *et al.* found this power index to amount to 2.3 ($\pm$ 1.1) $W \cdot ml^{-2} \cdot 10^4$. Sharir's data are not in the same range as the data reported from our series of patients. In Sharir's collective, however, LV-EDV was more than twice as high ($\approx$ 250 ml) compared with the patients investigated in this study. This fact points to severely impaired LV systolic function of those subjects and explains for their lower PWR_{max}/EDV^2 values. A close relationship between LV-EDV, an indication of preload, and PWR_{max}/EDV^2, a measure of contractile force, should be anticipated because the poorer contractile performance is, the more the ventricle will exploit its preload reserve by the Frank-Starling mechanism. Against this background it is not surprising that a fair inverse relation was dissolved between LV-EDV and PWR_{max}/EDV^2, with data best fit by an inverse equation (fig. 9).

Previous studies in humans have attempted to assess LV contractility by means of load-independent measures. Negative inotropic effects of propofol were suggested by some of these clinical trials,[14-16] whereas others reported preserved LV contractile function.[17,41] Disparity of the findings may in part be attributable to differences in study design. Nevertheless, disagreement surprises with respect to meth-

Table 2. Impact of the Lowest Plasma Concentrations of Propofol

	Control 0 (0.00 μg · ml^{-1}) (mean ± SD)	Control 1 (0.65 μg · ml^{-1}) (mean ± SD)	Study Group (0.65 μg · ml^{-1}) (mean ± SD)	*P* values	
				Paired *t* test (Control 0 *vs.* Control 1)	Independent Samples *t* Test (Control 1 *vs.* Study group)
PWR_{max}	5.30 ± 1.29	4.92 ± 1.27	5.05 ± 1.53	0.123	0.764
PWR_{max}/EDV^2	3.87 ± 1.48	3.97 ± 1.57	3.90 ± 1.75	0.584	0.155
LV-ESWS	65 ± 25	58 ± 25	58 ± 29	0.169	0.805
LV-EDV	122 ± 21	121 ± 22	122 ± 33	0.291	0.730

PWR_{max} = maximal power; PWR_{max}/EDV = preload adjusted maximal power; LV-ESWS = left ventricular end-systolic wall stress; LV-EDV = left ventricular end-diastolic volume.

odological approaches, which are all deduced from the same conceptual basis, namely from analysis of the end-systolic pressure-volume relationship (ESPVR) of the LV. Clearly, in experimental medicine the slope of the ESPVR has gained widespread acceptance as an indication of contractility.[42] But its precise determination necessitates both an invasive instrumentation of the LV to simultaneously register LV pressure and volume and a generation of profound changes in loading conditions by transient balloon occlusion of the inferior caval vein to create a series of variably loaded heart beats. Different clinically appealing approximations to reconstruct the ESPVR have been engaged in the literature, in an attempt to simplify data acquisition, and to restrict invasiveness to intraarterial pressure monitoring. These efforts may introduce an imminent source of inaccuracy in skillful ESPVR determinations.

Several inherent dilemmas of the clinical approximations should be addressed. First, substituting peak-systolic arterial pressure for end-systolic LV pressure seems to be doubtful.[15,16,41] By calculating the ratio of peak-systolic pressure and end-systolic LV dimension, two different times in the cardiac cycle are merged. Furthermore, the reliance on peripheral radial pressure, which is subject to frequent wave reflections, accentuates the problem. Second, contractile changes are not only mirrored in the slope of the ESPVR, but also in position shifts of the complete relation in the pressure-volume plane. Indicating systolic chamber function solely by the slope of the ESPVR may be inadequate. Changes in arterial resistance, as they occur during propofol infusions, tend to shift the complete ESPVR but have little effect on the slope of the line.[35] It is the volume axis intercept, referred to as the volume at which the left ventricle would generate no pressure, that is expected to vary under such a condition, and the assumption of a constant ventricular dead volume may be erroneous. Third, to avoid potential hazardous situations for the patients, analysis of the ESPVR is limited to a relatively small range of pressures and volumes, and the volume axis intercept is clinically always determined by extrapolation. As a consequence of extrapolation in many clinical studies the dead volume is negative. This apparent physiologic impossibility pinpoints the problems surrounding ESPVR determination in humans by relatively noninvasive

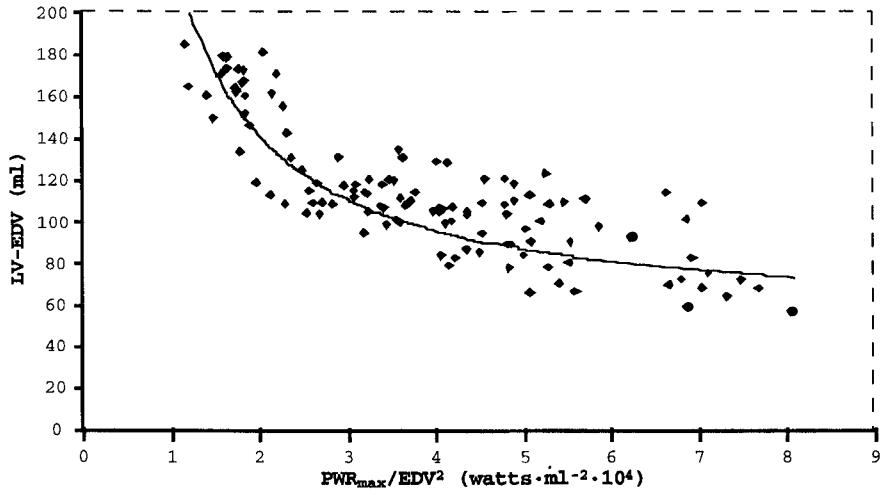

Fig. 9. Regression statistics with subsequent curve estimation: Maximal ventricular power divided by the square of end-diastolic ventricular volume (PWR_{max}/EDV^2) *versus* left ventricular end-diastolic volume (LV-EDV). The covariation is best explained by an inverse equation with r = 0.85, r^2 = 0.73, SEE = 16.19, *P* = 0.000.

means. Finally, it is worth contrasting the relative complexity of ESPVR determinations as opposed to the salient simplicity of PWR_{max}/D^2 estimations. In our opinion the chief advantage of PWR_{max}/D^2 as an indication of contractile strength in clinical practice is that this measure can be calculated from data obtained from a single cardiac cycle during steady-state conditions.

In the current investigation propofol decreased LV end-diastolic chamber dimension in humans after CABG surgery. This result shows that venodilation and LV preload reduction are important hemodynamic features of propofol. Our findings were previously confirmed by results in patients with coronary artery disease,[43] and they are unequivocally documented in patients with artificial hearts.[4]

LV-ESWS, E_a, and SVRI as indicators of LV afterload all decreased in a dose-related manner during propofol infusion. Previous reports described either propofol-induced reductions in SVR,[44] unchanged,[43] or even increased[45] SVR. Nevertheless, arterial vasodilation was demonstrated in patients with artificial hearts.[4]

Limitations of the Study

The present study contains limitations. First, when we completed the study, we reconsidered that we had designed it without collecting baseline data. Hence, we went back and did a further comparison of the impact of the lowest dose of propofol *versus* baseline in a separate control group. However, in view of the results obtained from the control group, the effect of the lowest plasma concentration appeared small or even negligible.

Second, it is conceivable that propofol's depressive hemodynamic effects *in vivo* are mediated *via* multiple mechanisms. Among these mechanisms the resetting of the baroreflex activity and inhibition of the sympathetic nervous system outflow are important and may contribute to preload, afterload, or inotropic drug response. Autonomic blockade is not performed in clinical scenarios. Thus, possible effects of the autonomic nervous system on measures of contractile function could not be eliminated. What the study demonstrates is that in a clinical setting propofol sedation does not depress contractile function, whether there is compensation from the autonomic nervous system or not.

Third, a fluid-filled catheter system was used to measure aortic pressures. This could have resulted in false high or low arterial pressure readings. Furthermore, time intervals might have been delayed when compared with measurements by micromanometers. Whereas the former is considered to be of minor importance because the pressure-transducer systems conformed to the dynamic responses recommended for clinical systems, the latter may have affected PWR_{max} determinations to some extent. However, we chose a technique to measure central arterial pressure, which was as close to clinical practice as possible.

Conclusions

PWR_{max}/D^2 appears to be a physiologically significant method to serially quantify LV contractility. PWR_{max}/D^2 can be rapidly assessed during surgery and on the ICU. Based on PWR_{max}/D^2 estimations propofol sedation does not exert overt negative inotropic actions in patients after CABG surgery. Prevalent hypotension should not be regarded as an inevitable side effect caused by a depression of contractile function but as a consequence of inappropriate ventricular loadings.

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