Moderate Acute Isovolemic Hemodilution Alters Myocardial Function in Patients with Coronary Artery Disease

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BACKGROUND: Although moderate hemodilution is usually well tolerated in coronary artery surgery patients, this may not be the case when myocardial oxygen demand is increased. We hypothesized that, in these patients, hemodilution in the presence of an increased heart rate could be associated with an impairment of myocardial function.

METHODS: Forty coronary surgery patients were randomly assigned to two groups ($n = 20$), according to the rate of atrioventricular pacing [70 bpm (Group 70) or 90 bpm (Group 90)]. While paced at the fixed heart rate, hemodilution was performed before the start of cardiopulmonary bypass. Data were obtained from a pulmonary artery, a PiCCO catheter and a left ventricular pressure catheter. Measurements were obtained in steady-state conditions before and after isovolemic hemodilution.

RESULTS: Hemodilution from 40% ± 2% to 30% ± 1% in Group 70, and from 39% ± 4% to 30% ± 2% in Group 90 resulted in a decrease in systemic vascular resistance and an increase in end-diastolic volume in both groups. This was associated with an increase in stroke volume in Group 70 but not in Group 90. In this latter group, the maximal rate of pressure development decreased significantly after hemodilution [from 856 ± 93 to 716 ± 80 mm Hg/s ($P < 0.01$)], whereas it remained unchanged in Group 70 (843 ± 86 mm Hg/s before and 832 ± 79 mm Hg/s after hemodilution).

CONCLUSIONS: In the conditions of the present study, increased heart rate during moderate hemodilution was associated with a depression of myocardial function.

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Tolerance to acute isovolemic hemodilution (AIH) in patients with coronary artery disease remains a controversial issue. In these patients, a lower hemoglobin was shown to be associated with an increased incidence of intra- and postoperative myocardial ischemia. In the presence of tachycardia (heart rate >100 bpm), this incidence was even higher, indicating that tolerance to isovolemic hemodilution may be further reduced when myocardial oxygen demand is increased.[1] Other studies, on the contrary, have shown that coronary artery surgery patients can tolerate moderate hemodilution without impairment of myocardial function.[2–5] This has been attributed to a lower rate-pressure product after hemodilution, mainly related to a decrease in heart rate.[5] Indeed, in contrast to awake patients in whom heart rate increases with hemodilution,[6] this response is blunted in anesthetized patients.[7] As heart rate is one of the major determinants of myocardial oxygen demand, its response to any intervention may greatly influence the tolerance to hemodilution.

We hypothesized that, especially in patients with severe coronary artery disease, the effects of moderate isovolemic hemodilution on myocardial function are influenced by the level of myocardial oxygen demand. To test this hypothesis, we studied left ventricular (LV) performance during moderate AIH [target hematocrit (HCT) of 30%] in coronary artery surgery patients at two different heart rates (70 and 90 bpm).

METHODS

Patient Population

The study was approved by the Institutional Ethical Committee (University Hospital Antwerp, Edegem, Belgium), and written informed patient consent was obtained. Forty patients with three-vessel coronary

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artery disease scheduled to undergo elective coronary artery surgery with cardiopulmonary bypass were included in the study. Preoperative exclusion criteria included previous coronary surgery or valve replacement, combined operations (simultaneous valve repair and coronary surgery, carotid endarterectomy, or LV aneurysm repair), unstable angina, documented myocardial infarction within the previous 6 wk, active congestive heart failure, hemodynamic instability with the need for medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >150 U/L), renal insufficiency (creatinine concentration >1.5 mg/dL), severe chronic obstructive pulmonary disease (forced expired volume in 1 s <0.8 L), or history of neurologic disturbance, age >80 yr and a preoperative HCT <36.

Study Groups

Patients were randomly allocated to two different groups using a computer-generated random code. The participant randomization assignment was concealed in an envelope until after anesthesia induction. In the first group (Group 70: $n = 20$), heart rate was paced at 70 bpm, and in the second group (Group 90: $n = 20$), heart rate was paced at 90 bpm.

Anesthesia and Surgery

Antiplatelet therapies were stopped 1 wk before the operation and replaced by a daily dose of nadroparine (Fraxiparine®; Sanofi-Synthelabo, Brussels, Belgium), 0.6 mL (7500 U anti-Xa) subcutaneously. Sulfonylurea derivatives were stopped 2 days before the operation and replaced by insulin therapy if necessary. Angiotensin-converting enzyme inhibitors and the angiotensin II receptor antagonists were also stopped 2 days before surgery. All other preoperative cardiac medication (β-blockers, statins, calcium-blocking drugs, nitrates) was continued until the morning of surgery.

Premedication was standardized for all patients (2.5 mg sublingual lorazepam [Temesta Expidet®; AHP Pharma, Louvain-la-Neuve, Belgium] 90 min before surgery and 1 μg/kg fentanyl plus 50 μg/kg droperidol, given IM 60 min before surgery). In the operating room, patients received routine monitoring, including 5-lead electrocardiogram (ECG), radial and pulmonary artery catheters with continuous cardiac output (CO) measurement, pulse oxymetry, capnography, and blood and urine bladder temperature monitoring. In all patients, a PiCCO catheter (PiCCO plus, Pulsion Medical Systems, Munich, Germany) was inserted in the left femoral artery. This is a device that quantifies several variables, including continuous (pulse contour) CO and derived variables, cardiac preload, systemic vascular resistance (SVR), and extravascular lung water. The patient requires a central venous line in the internal jugular or subclavian vein (in this study the right atrial port of the Swan Ganz catheter), and an arterial catheter with a thermistor in one of the larger arteries of the body (in this study the femoral artery). The principle is that a known volume of a thermal indicator (20 mL ice-cold saline) is injected into the central vein. The injectate rapidly disperses within the pulmonary and cardiac volumes (intrathoracic volume). When the thermal signal reaches the arterial thermistor, a temperature difference is detected and a dissipation curve is generated on which CO is calculated. PiCCO data were used for the determination of end-diastolic volume (EDV) and stroke volume (SV). In addition, a transesophageal echocardiography (TEE) probe (Agilent SONOS 5500, Brussels, Belgium) was positioned at the midpapillary level of the LV in all patients to monitor occurrence of regional wall motion abnormalities.

Anesthesia was induced with a continuous infusion of remifentanil 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.1 mg/kg midazolam. Muscle paralysis was obtained with 0.15 mg/kg cisatracurium. Anesthesia was maintained with 0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ midazolam. Depth of anesthesia was monitored with bispectral index (BIS XP®; Aspect Medical Systems, Newton, MA) and aimed at a bispectral index between 40 and 50 during surgery.

Standard median sternotomy and pericardiotomy were performed. After administration of 300 IU/kg heparin, the aortic and venous cannula were secured in place. The priming fluid of the extracorporeal circulation circuit contained 1000 mL 6% hydroxyethyl starch 130/0.4 (Voluven®, Fresenius Kabi, Schelle, Belgium), and 300 mL crystalloids (Plasma-Lyte®, Baxter, Lessines, Belgium).

Study Protocol

After induction, heart rate varied between 45 and 65 bpm. After the opening of the pericardium, atrial and ventricular pacing wires were put in place and pacing was started according to the randomization. In Group 70, heart rate was kept constant by atrioventricular pacing at a rate of 70 bpm and in Group 90 at a rate of 90 bpm. In all patients, the atrioventricular interval was set at 150 ms. None of the patients had documented sinus node disease or had signs of atrioventricular conduction abnormalities on preoperative ECG. After the surgical preparation (harvesting of the mammary artery, cannulation and positioning of the LV pressure catheter), an additional 5 min stabilization period was allowed. As a consequence, all patients were paced for about 20 min (range 15–22 min) before the AIH procedure was started. In none of the patients, were signs of myocardial ischemia observed on ECG or TEE.

Anesthesia before and during the hemodilution procedure was kept constant in all patients: 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ midazolam. Blood was harvested before cardiopulmonary bypass via the venous cannula and substituted with the same amount of pump prime. The amount of blood withdrawn was calculated to reach a calculated

HCT of 24% on cardiopulmonary bypass using the following equation[8]:

$$\frac{(\text{EBV} - \text{ABW}) \times \text{Hct}}{\text{EBV} - (\text{ABW} + \text{RV}) + \text{PV}} = 24\%$$

where EBV is estimated blood volume (calculated as body weight multiplied 65 mL/kg for women and by 70 mL/kg for men), ABW is autologous blood volume to be withdrawn, RV is the replacement volume (=ABW), Hct = preoperative hematocrit, and PV is prime volume. The target HCT of 24% on cardiopulmonary bypass was chosen to have a sufficient margin of safety in HCT values when mixing with the priming fluid had occurred after the start of cardiopulmonary bypass, thus to avoid the need for transfusion. The hemodilution procedure was standardized in all patients to take 15 min. During this period, the blood was gradually harvested and replaced by the same amount of cardiopulmonary bypass fluid with a stable central venous pressure (CVP) and pulmonary capillary wedge pressure as guidelines to prevent abrupt changes in volume status. After AIH, a 5-min stabilization period was allowed before the measurements were obtained.

Measurements

After the venous cannulation, a sterilized prezeroed electronic tipmanometer (Millar MTCP3Fc catheter; Dräger Medical Electronics, Best, The Netherlands; frequency response = 100 KHz) was inserted in each patient in the LV through the left superior pulmonary vein. The catheter was connected to a Hewlett Packard monitor (HP78342A; Hewlett Packard, Brussels, Belgium). The output signals of the pressure transducer system were digitally recorded together with the ECG signals at 1 ms intervals (Codas; DataQ, Akron, OH). Zero and gain setting of the tipmanometer were checked against a high-fidelity pressure gauge (Druck Ltd., Leicester, United Kingdom) after removal.

All measurements were obtained with the ventilation suspended at end-expiration. The measurements consisted of recordings of consecutive ECG and LV pressure tracings during an increase of systolic and diastolic pressures obtained by raising the caudal part of the surgical table by 45 degree, resulting in raising of the legs. Leg elevation resulted in a rapid beat-to-beat increase in LV pressures. A first set of measurements was obtained before AIH, and a second set of measurements after 5 min steady-state after the end of the hemodilution procedure.

Hemodynamic Data Analysis

Global hemodynamic data (mean arterial blood pressure, mean pulmonary artery pressure, CVP, CO, and SVR) and PiCCO-derived EDV and SV data were also recorded before and after AIH.

LV data were recorded before and after isovolemic hemodilution. End-diastolic pressure (EDP) was timed at the peak of the R wave on the ECG. The effects of leg elevation in the different conditions were evaluated by the changes in EDP, peak LVP pressure (LVP), LVP at dP/dt_{min} [=end-systolic pressure (ESP)], and dP/dt_{max}. Effects of leg elevation on rate of LVP decrease were evaluated by dP/dt_{min} and the time constant τ of isovolumic relaxation. τ was calculated based on the monoexponential model with the nonzero asymptote using LVP values from dP/dt_{min} to a pressure 10 mm Hg above LVEDP. The following equation was used: $\ln P_t = \ln P_0 - \text{time}/\tau$. Time constant τ was fit in a linear manner to the corresponding ESP, and the slope R (ms/mm Hg) of this relation was calculated. R quantified changes in τ, induced by the changes in ESP and quantified afterload dependence of the rate of LVP decrease. At least 10 consecutive beats were taken for the calculation of R. Sample correlation coefficients of the ESP-τ relationships yielded values of $r > 0.92$ in all patients. Previous reports have indicated that such analysis provides accurate information on systolic and diastolic function and allows assessment of the functional reserve capacity of the LV under various circumstances.[9–15]

Arterial and mixed venous blood samples were analyzed for the calculation of the different variables of oxygen transport. The blood samples were taken before and 5 min after isovolemic hemodilution.

Statistical Analysis

The primary outcome variable in the present study was the change in dP/dt_{max} with AIH. A minimum detected difference of 50 mm Hg/s between groups was considered clinically significant. For a power of 0.8 and $\alpha = 0.01$, a sample size of 20 patients in each group was calculated to be appropriate.

Hemodynamic and oxygen variables were tested for normal distribution using the Kolmogorov-Smirnov test. Data were analyzed using a two-way analysis of variance for repeated measurements. This allowed assessment of the effects of treatment (isovolemic hemodilution). Interaction analysis revealed whether these effects were different between groups. Post-test analysis was performed using the Bonferroni-Dunn test. Patient characteristics and postoperative data were compared using analysis of variance. Post-test analysis was performed using the Tukey-test. All data were expressed as mean ± SD, unless noted otherwise. Statistical significance was accepted at $P < 0.01$.

RESULTS

There were no significant differences in demographic and intraoperative data between the groups (Table 1). In both groups HCT decreased significantly after AIH (from 40 ± 2 to 30 ± 1 in Group 70, and from 39 ± 4 to 30 ± 2 in Group 90). No ischemic alterations on ECG or new regional wall motion abnormalities

Table 1. Demographic and Intraoperative Data

	Group 70	Group 90
Demographic data		
Gender (male/female)	16/4	17/3
Age (yr)	65 ± 8	68 ± 10
Weight (kg)	87 ± 9	86 ± 14
Length (cm)	174 ± 6	175 ± 6
BSA(m^2)	2.0 ± 0.1	2.0 ± 0.2
Previous myocardial infarction	8	8
EF (%)	61 ± 12	65 ± 10
Diabetes	3	3
ES add, median (range)	2 (0 – 5)	3 (0 – 6)
ES log, median (range)	1.5 (0.88 – 4.67)	2.4 (0.88 – 4.86)
Hct preop	41 ± 3	39 ± 4
Preoperative medication		
β-blockers	17	17
Calcium channel blockers	6	6
ACE inhibitors	8	8
AT II receptor antagonists	3	2
Intraoperative data		
No. of grafts, median (range)	4 (2 – 6)	4 (2 – 6)
No. of arterial grafts, median (range)	1 (1 – 2)	1 (1 – 3)
Aortic crossclamp time	30 ± 9	36 ± 16
CPB time	82 ± 17	102 ± 22
Predonation volume (mL)	1076 ± 176	952 ± 209

Data are presented as mean ± SD, unless noted otherwise. There were no differences between the two groups in any of the preoperative and intraoperative patient characteristics.

BSA = body surface area; EF = ejection fraction; ES = Euroscore = European System for Cardiac Operative Risk Evaluation; Hct = hematocrit; ACE = angiotensin converting enzyme; AT II = angiotensin II; CPB = cardiopulmonary bypass.

were reported on TEE monitoring during the period of pacing and of the isovolemic hemodilution procedure.

Hemodynamic data are summarized in Table 2. Atrioventricular pacing did not alter SV nor filling pressures. In both groups, hemodilution resulted in a significant decrease in SVR and a significant increase in EDV, whereas mean arterial blood pressure, CVP, mean pulmonary artery pressure, and EDP remained unchanged. SV increased in Group 70 but not in Group 90. In this latter group, dP/dt_{max} decreased from 856 ± 93 to 716 ± 80 mm Hg/s ($P < 0.01$), whereas in Group 70, dP/dt_{max} remained unchanged. Figure 1 displays the individual changes in dP/dt_{max} before and after hemodilution in both groups. In Group 90, all patients had a decrease in dP/dt_{max} with hemodilution, whereas in Group 70 some patients showed an increase, some a decrease and some no change in dP/dt_{max}. The time constant of isovolumic relaxation τ remained similar before and after hemodilution in Group 70 but increased in Group 90 indicating slowing of myocardial relaxation (Table 3). A similar phenomenon was observed for τ as for dP/dt_{max}. In Group 90, all patients had an increase in τ with hemodilution, whereas in Group 70 some patients showed an increase, some a decrease and some no change in τ.

In Group 70, leg elevation resulted in a similar change in dP/dt_{max} before and after hemodilution, indicating preserved load-dependent myocardial function whereas in Group 90, leg elevation after

Table 2. Hemodynamic Data Before Cardiac Pacing, and Before and After Acute Isovolemic Hemodilution

	Before cardiac pacing	Before hemodilution	After hemodilution
HR (bpm)			
Group 70	55 ± 6	70	70
Group 90	58 ± 8	90	90
MAP (mm Hg)			
Group 70	70 ± 6	71 ± 4	68 ± 7
Group 90	72 ± 7	74 ± 7	72 ± 7
CVP (mm Hg)			
Group 70	12 ± 4	12 ± 3	13 ± 3
Group 90	11 ± 4	11 ± 3	11 ± 3
MPAP (mm Hg)			
Group 70	22 ± 5	20 ± 4	23 ± 4
Group 90	22 ± 4	20 ± 3	21 ± 3
SV (mL)			
Group 70	62 ± 9	66 ± 10	80 ± 11*†
Group 90	65 ± 11	64 ± 10	64 ± 10
CO (mL/min)			
Group 70	3.8 ± 0.9	4.2 ± 0.7†	5.7 ± 0.9*
Group 90	4.0 ± 0.8	5.6 ± 0.6	5.3 ± 1.0
SVR ($dynes \cdot s \cdot cm^{-5}$)			
Group 70	1064 ± 233	1149 ± 306	897 ± 222*
Group 90	1029 ± 178	981 ± 203	791 ± 156*
EDV (mL)			
Group 70	1082 ± 195	1146 ± 235	1588 ± 419*
Group 90	1115 ± 225	1079 ± 251	1404 ± 297*

Data are presented as mean ± SD.

HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; MPAP = mean pulmonary arterial pressure; SV = stroke volume; CO = cardiac output; SVR = systemic vascular resistance; EDV = end-diastolic volume.

* Statistically significant difference compared with the before hemodilution value.

† Statistically significant difference between groups ($P < 0.01$).

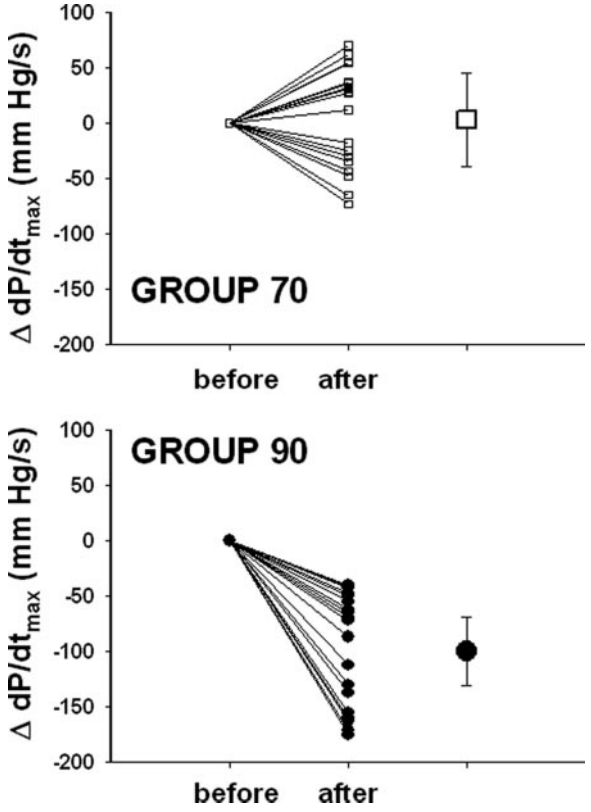

Figure 1. Change (Δ) in the maximal rate of pressure development (dP/dt_{max}) with acute isovolemic hemodilution in the individual patients of the two groups. In Group 70, the response varied between a decrease, no change or an increase in dP/dt_{max}, whereas in Group 90 all patients had a decrease in dP/dt_{max}, indicating impairment of myocardial function after hemodilution.

Table 3. Left Ventricular Pressure Data Before and After Acute Isovolemic Hemodilution

	Before hemodilution	After hemodilution
EDP (mm Hg)		
Group 70	10 ± 3	12 ± 5
Group 90	10 ± 4	14 ± 3
Peak LVP (mm Hg)		
Group 70	84 ± 7	85 ± 10
Group 90	91 ± 9	88 ± 6
dP/dt_{max} (mm Hg/s)		
Group 70	843 ± 86	832 ± 79
Group 90	856 ± 93	716 ± 80*†
dP/dt_{min} (mm Hg/s)		
Group 70	−650 ± 123	−616 ± 124
Group 90	−654 ± 65	−661 ± 69
ESP (mm Hg)		
Group 70	55 ± 11	51 ± 9
Group 90	57 ± 9	55 ± 6
τ (ms)		
Group 70	62 ± 5	63 ± 5
Group 90	61 ± 4	69 ± 4*†

Data are presented as mean ± SD.

EDP = end-diastolic pressure; LVP = left ventricular pressure; dP/dt_{max} = maximal rate of left ventricular pressure development; dP/dt_{min} = maximal rate of left ventricular pressure decline; ESP = end-systolic pressure; τ = time constant of isovolumic relaxation.

* Statistically significant difference compared with the before hemodilution value.

† Statistically significant difference between groups ($P < 0.01$).

Table 4. Changes in Left Ventricular Pressure Data with Leg Elevation Before and After Acute Isovolemic Hemodilution

	Before hemodilution	After hemodilution
Δ EDP (mm Hg)		
Group 70	3 ± 2	3 ± 2
Group 90	3 ± 2	5 ± 2
Δ Peak LVP (mm Hg)		
Group 70	10 ± 5	8 ± 6
Group 90	9 ± 5	8 ± 4
Δ dP/dt_{max} (mm Hg/s)		
Group 70	40 ± 35	47 ± 22
Group 90	54 ± 38	−38 ± 23*†
Δ dP/dt_{min} (mm Hg/s)		
Group 70	−55 ± 21	−42 ± 54
Group 90	−53 ± 33	−50 ± 45
Δ ESP (mm Hg)		
Group 70	8 ± 6	5 ± 5
Group 90	6 ± 4	6 ± 3
Δ τ (ms)		
Group 70	1 ± 3	2 ± 2
Group 90	1 ± 1	5 ± 2*†
R (ms/mm Hg)		
Group 70	0.2 ± 0.3	0.2 ± 0.3
Group 90	0.1 ± 0.1	0.7 ± 0.2*†

Data are presented as mean ± SD.

EDP = end-diastolic pressure; LVP = left ventricular pressure; dP/dt_{max} = maximal rate of left ventricular pressure development; dP/dt_{min} = maximal rate of left ventricular pressure decline; ESP = end-systolic pressure; τ = time constant of isovolumic relaxation; R = afterload dependence of left ventricular pressure decrease.

* Statistically significant difference compared with the before hemodilution value.

† Statistically significant difference between groups ($P < 0.01$).

hemodilution resulted in a significant decrease in dP/dt_{max} ($\Delta dP/dt_{max}$ before hemodilution: 54 ± 38 mm Hg vs Δ dP/dt_{max}: −38 ± 23 mm Hg after hemodilution ($P < 0.01$), indicating an impairment of load-dependent regulation of myocardial function. The change in τ with leg elevation was similar before and after hemodilution in Group 70. In Group 90, however, the increase in τ with leg elevation after hemodilution was significantly higher than before. Load dependence of relaxation R was similar before and after hemodilution in Group 70, but increased significantly in Group 90 (Table 4).

In Group 70, hemodilution was associated with an increase in SV which compensated for the reduction of CaO_2. As a result, oxygen delivery (DO_2) remained stable in this group. In Group 90, SV did not increase and DO_2 decreased significantly. In both groups, oxygen consumption (VO_2) remained constant during the entire observation period. Oxygen extraction increased from 19% ± 1% to 24% ± 2% in Group 90, but remained unchanged after hemodilution in Group 70 (Table 5).

DISCUSSION

The results of the present study indicate that, in coronary artery disease patients under general anesthesia, moderate isovolemic hemodilution can be associated with an impairment of myocardial function in

Table 5. Blood Gas Values Before and After Acute Isovolemic Hemodilution

	Before ANH	After ANH
DO_2 (mL O_2/min)		
Group 70	733 ± 137†	770 ± 164
Group 90	922 ± 91	695 ± 128*
VO_2 (mL O_2/min)		
Group 70	178 ± 45	166 ± 42
Group 90	172 ± 29	159 ± 29
CaO_2 (mL/dL blood)		
Group 70	18 ± 1	14 ± 1*
Group 90	17 ± 2	13 ± 1*
CvO_2 (mL/dL blood)		
Group 70	14 ± 1	11 ± 1*
Group 90	14 ± 2	10 ± 1*
Δ AV (mL/dL blood)		
Group 70	4 ± 1	3 ± 1
Group 90	3 ± 1	3 ± 1
O_2 extraction (%)		
Group 70	20 ± 5	21 ± 6
Group 90	19 ± 1	24 ± 2*
Hct (%)		
Group 70	40 ± 2	30 ± 1*
Group 90	39 ± 4	30 ± 2*

Data are presented as mean ± SD.

DO_2 = oxygen delivery; VO_2 = oxygen consumption; CaO_2 = arterial oxygen content; CvO_2 = venous oxygen content; Δ AV = arteriovenous difference in O_2 content; Hct = hematocrit.

* Statistically significant difference compared with the before hemodilution value.

† Statistically significant difference between groups ($P < 0.01$).

the presence of increased myocardial work associated with a heart rate of 90 instead of 70 bpm.

With hemodilution, SV normally increases because of a decrease in SVR (decreased viscosity of the blood) and an increase in EDV (increased venous return).[16] In the present study, this was observed in Group 70 but not in Group 90, where SV remained constant despite the expected changes in SVR and EDV. This observation suggested deterioration of myocardial function in this group. This was confirmed by the analysis of LVP-derived data. In contrast to Group 70, isovolemic hemodilution was associated in all patients of Group 90 with a decrease in dP/dt_{max}, as a measure of systolic function and an increase of time constant τ of isovolumic relaxation, as a measure of diastolic function. The ability of the heart to respond to an increased load was also impaired in these patients. This was evident from the decrease in dP/dt_{max}, the slowing of myocardial relaxation and the increased load dependence of myocardial relaxation with leg elevation, indicating an increase in relative load at which the ventricle is working.[9–15] It is important to note that this phenomenon already occurred after a moderate hemodilution to a hematocrit value of about 30%. The present results, therefore, confirm the hypothesis that tolerance of the heart to hemodilution is closely related to the determinants of myocardial oxygen demand, among which heart rate is an important factor.[16]

The present results seem to be in contrast to some reports demonstrating that coronary artery surgery patients can tolerate moderate hemodilution without impairment of myocardial function.[2–5] These results were attributed to a lower rate-pressure product after AIH, mainly related to a decrease in heart rate.[5] Several studies have indeed shown that, in anesthetized patients, moderate hemodilution is associated with a decrease in heart rate,[2,3,5,7] which is in contrast to what happens in awake patients or volunteers in whom heart rate increases with hemodilution.[6] For the present study, we aimed to avoid the hemodynamic and metabolic effects of heart rate changes by maintaining this variable constant during hemodilution. By pacing the hearts at constant rate, we were able to identify the intimate relationship between heart rate and tolerance to hemodilution.

Another observation from the present study was that hemodilution was associated with a significant increase in EDV but with no significant concomitant increase in EDP. However, when observing the relative changes in volumes and pressures with hemodilution, it seems that the ratio ΔV on ΔP with hemodilution in Group 90 differed from this ratio in Group 70 [ΔV/ΔP (mL/mm Hg): 98 ± 104 vs 409 ± 147 ($P < 0.01$)], which may indicate a decreased LV compliance in Group 90. Unfortunately, true LV compliance could not be calculated before and after hemodilution because of limitations of the PiCCO technology (insufficient sampling rate).

This study should be interpreted within the constraints of several methodological issues. It was hypothesized that in patients with severe coronary artery disease, the effects of moderate isovolemic hemodilution on myocardial function are influenced by the level of myocardial oxygen demand. The results of the present study did indeed demonstrate that moderate hemodilution in coronary surgery patients was associated with an impairment of myocardial function at heart rates of 90 bpm. Although it can be expected that more rapid heart rates are associated with an increase in cardiac workload, hence an increase in myocardial oxygen demand, there are no direct data demonstrating that this was indeed the case. Direct blood sampling from the coronary sinus would have provided more unequivocal evidence for an increased myocardial VO_2 and would have allowed detection of a possible occurrence of myocardial oxygen supply–demand mismatch with moderate hemodilution at faster heart rates. Five-lead ECG was monitored throughout. However, since patients were paced in atrioventricular mode throughout the study period, morphology of the QRS complex and the ST-segment differed from the normal pattern and rendered diagnosis of ischemia based on ST-segment changes hazardous. Atrial pacing would have yielded a more reliable assessment of potential ischemic changes but would have carried the risk of intermittent rhythm disturbances related to atrioventricular conduction problems. Since part of the hemodynamic analysis in the present study depended on a beat-to-beat analysis of myocardial function, there was need for a regular

heart rate without extrasystoles, which was the reason why the atrioventricular pacing mode was chosen. With this in mind, no ECG changes were observed throughout the study period. TEE was used as a monitor for the occurrence of regional wall motion changes, none of which occurred during the study period. However, it should be noted that this tool was only used as perioperative monitoring, and therefore no data were recorded for *post hoc* analysis. In addition, only the short-axis view of the LV was monitored, thereby limiting the number of observed segments. Collection of transmitral and pulmonary venous flow signals for *post hoc* analysis might have provided additional information.

The effects of isovolemic hemodilution on myocardial contractile function were assessed using dP/dt_{max} and the changes in dP/dt_{max} with increase in cardiac load (leg elevation) before and after hemodilution reflecting the potential changes in the functional reserve capacity of the LV.[9–15] In patients with a good ventricular function, dP/dt_{max} increases with leg elevation, whereas it does not change in patients with moderate function and decreases in patients with impaired ventricular function, reflecting impairment of the contractile function of the heart. A typical coronary surgery population shows the entire spectrum of responses.[9,10] This was also observed in both groups before hemodilution. After hemodilution, the response of dP/dt_{max} to leg elevation remained unchanged in Group 70, but was significantly reduced in Group 90. Measurement of systolic pressure–volume relationships with calculation of ventricular elastance would have provided additional direct information on myocardial contractility. However, this requires the use of conductance catheters, which is a more invasive methodology. Alternatively, data from pressure measurements could be combined with TEE-derived dimension data but this carries the limitation of lack of synchronization between pressure and dimension data due to the difference in sampling rate, ultimately yielding unreliable conclusions.

The effects of isovolemic hemodilution on diastolic function were assessed by analysis of the rate of myocardial relaxation. A slowing of myocardial relaxation (increase in τ) and an increase of the load dependence of myocardial relaxation was observed. Myocardial relaxation is an active process and becomes very quickly impaired, for instance during demand ischemia such as may occur with increased heart rate.[17–19]

Recently two papers from the same group have indicated that isovolemic hemodilution was associated with a lower postoperative troponin I release in cardiac surgery patients.[5,20] The authors suggested that the optimization of the myocardial DO_2 and/or $VO_2$and possible postconditioning effects of endogenous erythropoietin might have contributed to the observed cardioprotection with hemodilution. Such beneficial effect of hemodilution, however, may not be present when heart rate does not decrease but remains elevated for some other pathophysiological reason, such as hypovolemia, pain, shivering, and arousal from anesthesia. Our results do indeed demonstrate that even moderate hemodilution might result in an impairment of myocardial function in case of increased heart rate.

In the present study, patients were paced at two different heart rates to standardize this determinant of myocardial work. Heart rates of 70 and 90 bpm, however, are rapid rates for coronary surgery patients. It can therefore not "a priori" be excluded that some patients in the present study population may have developed myocardial ischemia as a consequence of the high heart rates before the hemodilution procedure. Therefore, pacing was started from the moment that the wires could be applied on the atrial and ventricular wall, leaving sufficient stabilization time between the start of pacing and the start of the experimental protocol. In none of the patients were signs of myocardial ischemia or deterioration of myocardial function observed, which indicated that the pacing procedure was not the underlying reason for the different response with hemodilution between groups.

Although coronary surgery patients constitute a very specific surgical population, we chose to perform the study in this setting because of the following reasons. In these patients, coronary disease had been well documented. Second, the open chest situation allows control of heart rate in a very standardized way that is not possible in other patient populations. The data of this study indicated that in patients with coronary artery disease, performing moderate hemodilution (target Hct = 30%) in the presence of an increased myocardial DO_2 (heart rate = 90 instead of 70 bpm) may result in impairment of myocardial function.

Our results may have the following clinical implications. First, they indicate that hemodilution should be performed cautiously, also in noncardiac surgery patients whose potential extent of coronary artery disease is less well defined. In addition, anti-ischemic therapy is usually less controlled in such patients, making them more vulnerable to potential alterations in myocardial oxygen supply–demand ratios. Second, the close relationship between heart rate, as one of the determinants of myocardial DO_2 and the effects of hemodilution, which were observed in the present study, should prompt clinicians to re-evaluate the safe target HCT of coronary artery disease patients in view of the expected perioperative hemodynamic status.

In conclusion, the data of the current study indicated that AIH may result in myocardial dysfunction in specific situations associated with an increased heart rate.

REFERENCES

1. Hogue CW, Goodnough LT, Monk TG. Perioperative myocardial episodes are related to hematocrit level in patients undergoing radical prostectomy. Transfusion 1998;38:924–31
2. Spahn DR, Schmid ER, Seifert B, Pasch T. Hemodilution tolerance in patients with coronary artery disease who are receiving chronic β-adrenergic blocker therapy. Anesth Analg 1996;82: 687–94
3. Licker M, Ellenberger C, Sierra J, Christenson J, Diaper J, Moerel D. Cardiovascular response to acute normovolemic hemodilution in patients with coronary artery disease: assessment with transesophageal echocardiography. Crit Care Med 2005;33:591–7
4. Herregods L, Moerman A, Foubert L, Francois K, Rolly G. Limited intentional normovolemic hemodilution: ST-segment changes and use of homologous blood products in patients with left main coronary stenosis. J Cardiothorac Vasc Anesth 1997;11:18–23
5. Licker M, Ellenberger C, Sierra J, Kalangos A, Diaper J, Morel D. Cardioprotective effects of acute normovolemic hemodilution in patients undergoing coronary artery bypass surgery. Chest 2005;128:838–47
6. Weiskopf RB, Feiner J, Hopf H, Viele MK, Watson JJ, Lieberman J, Kelley S, Toy P. Heart rate increases linearly in response to acute isovolemic anemia. Transfusion 2003;43:235–40
7. Ickx B, Rigolet M, Van der Linden P. Cardiovascular and metabolic response to acute normovolemic anemia. Anesthesiology 2000;93:1011–6
8. Flom-Halvorsen HI, Ovrum E, Oystese R, Brosstad F. Quality of intraoperative autologous blood withdrawal used for retransfusion after cardiopulmonary bypass. Ann Thorac Surg 2003; 76:744–8
9. De Hert SG, Gillebert TC, ten Broecke PW, Mertens E, Rodrigus IE, Moulijn AC. Contraction-relaxation coupling and impaired left ventricular performance in coronary surgery patients. Anesthesiology 1999;90:748–57
10. De Hert SG, Gillebert TC, ten Broecke PW, Moulijn AC. Length-dependent regulation of left ventricular function in coronary surgery patients. Anesthesiology 1999;91:379–87
11. De Hert SG, Van der Linden PJ, ten Broecke PW, Rodrigus IE, Sermeus LA, Moulijn AC, Gillebert TC. The effects of β-adrenergic stimulation on the length-dependent regulation of myocardial function in coronary surgery patients. Anesth Analg 1999;89:835–42
12. De Hert SG, Vander Linden PJ, ten Broecke PW, Sermeus LA, Gillebert TC. Effects of nicardipine and urapidil on length-dependent regulation of myocardial function in coronary artery surgery patients. J Cardiothorac Vasc Anesth 1999;13:677–83
13. De Hert SG, ten Broecke PW, Rodrigus IE, Mertens E, Stockman BA, Vermeyen KM. The effect of the pericardium on length-dependent regulation of left ventricular function in coronary surgery patients. J Cardiothorac Vasc Anesth 2001;15:300–5
14. De Hert SG, Vander Linden PJ, ten Broecke PW, Vermeylen KT, Rodrigus IE, Stockman BA. Effects of Desflurane and Sevoflurane on length-dependent regulation of myocardial function in coronary surgery patients. Anesthesiology 2001;95:357–63
15. De Hert SG, ten Broecke PW, Mertens E, Rodrigus IE, Stockman BA. Effects of phosphodiesterase III inhibition on length-dependent regulation of myocardial function in coronary surgery patients. Br J Anaesth 2002;88:779
16. Van der Linden P, De Hert S. Normovolemic hemodilution of the heart. Can J Anaesth 2005;52:130–2
17. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation 1985;71:889–900
18. Gwathmey JK, Slawsky MT, Hajjar RJ, Briggs GM, Morgan JP. Role of intracellular calcium handling in force-interval relationships of human ventricular myocardium. J Clin Invest 1990; 85:1599–613
19. Grossman W. Diastolic dysfunction in congestive heart failure. N Engl J Med 1991;325:1557–64
20. Licker M, Sierra J, Kalangos A, Panos A, Diaper J, Ellenberger C. Cardioprotective effects of acute normovolemic hemodilution in patients with severe aortic stenosis undergoing valve replacement. Transfusion 2007;47:341–50