Metabolic flow regulation in human coronary artery disease

Kal, J.E.

Citation for published version (APA):
Chapter 6

Rate of coronary flow adaptation to changes in heart rate before and during anesthesia for coronary artery surgery

Anesthesiology 1996;84:1107-18
Abstract

Background. The rate of adaptation of coronary blood flow in response to stepwise changes in heart rate has been extensively studied in dogs and goats, in order to improve our understanding of the dynamics of coronary regulation processes, its pathophysiology and to obtain time constants for mathematical modeling of the coronary regulation. However, little is known about the dynamic characteristics of coronary flow adaptation in humans. In patients undergoing coronary artery surgery, we investigated the rate of coronary adaptation in response to stepwise changes in heart rate, in both the awake and anesthetized state.

Methods. In 11 patients with stable coronary artery disease, arterial blood pressure, right atrial pressure and coronary sinus blood flow, measured by continuous thermodilution, were calculated per beat. The ratio of beat averaged arterial blood pressure minus right atrial pressure and coronary sinus blood flow was calculated to obtain an index of coronary resistance. The rate of change of coronary resistance index was quantified by $t_{50}$, defined as the time required to establish 50% of the total change in coronary resistance index. Responses of coronary resistance index after heart rate changes, before and after induction of anesthesia, were compared. The anesthesia technique consisted of fentanyl 100 μg·kg⁻¹, pancuronium bromide 0.1 mg·kg⁻¹ in combination with oxygen in air ventilation ($F_{O_2}=0.5$).

Results. In the awake situation, $t_{50}$-values of the dilating and constricting responses, induced by an increase and decrease in heart rate were $5.0 \pm 2.1$ (SD) sec (range 2.6 to 9.0 sec), and $5.7 \pm 1.2$ sec (range 4.1 to 7.8 sec), respectively. During fentanyl/pancuronium anesthesia the rate of coronary flow adaptation was significantly slower, with $t_{50}$-values of $10.2 \pm 2.1$ sec (range 7.7 to 13.1 sec), after a heart rate step up and $9.8 \pm 2.1$ sec (range 6.6 to 13.2 sec), after a heart rate step down. Compared to the awake situation arterial blood pressure was significantly reduced during anesthesia, but coronary vascular resistance remained unchanged. This implies that the steady state static regulation of coronary blood flow had not changed.

Conclusions. These preliminary data suggest that in patients with coronary artery disease, the rate of change in coronary vascular resistance in response to pacing-induced changes in heart rate is mitigated by fentanyl/pancuronium anesthesia during positive pressure ventilation. A further qualification of our findings in a larger number of patients is warranted.
1. Introduction

In 1947, Eckenhoff et al. demonstrated that myocardial oxygen supply matches myocardial oxygen demand in steady state [1]. This finding was confirmed by a number of investigators, using different species of experimental animals [2-4]. The dynamic behavior of the coronary arterial system was first described by Belloni and Sparks in 1977 [5]. Using open chest dogs they calculated the time course of changes in coronary vascular resistance (CVR) in response to pacing induced changes in heart rate (HR). Using dogs and goats, Dankelman has shown that the rate of change of CVR can be quantified by a $t_{50}$ value, calculated from the ratio of beat averaged coronary perfusion pressure and coronary blood flow. This $t_{50}$ value varies in different species and can be influenced by drugs [6-8]. Neither in experimental animals nor in humans it is known whether there is a difference in the rate of coronary flow regulation during awake and anesthetized conditions, although the impact of anesthesia on the static relation between myocardial oxygen consumption (MVO$_2$) and coronary blood flow is well documented. [9-13] The effect of a faster or slower coronary response to changes in HR and MVO$_2$ on physiological and pathophysiological processes is also unknown. It is conceivable that especially in patients with coronary stenoses, too slow a response might lead to myocardial ischemia, while a faster response might preserve the ratio between myocardial oxygen supply and MVO$_2$. This may be a simplification, because the mechanism involved in regulation of coronary blood flow is a complex process involving several factors, including metabolic, myogenic, and neurohumoral regulation and endothelial responses [3,14-18].

The process can be described as a high order control system. These types of control systems can oscillate depending on phase shifts and amplification factors within the system [19]. It is therefore conceivable that the mechanism(s) involved in the dynamics of flow regulation and pathological processes, including coronary artery disease (CAD) and endothelial lesions, may interact with each other. Within such an interaction, a fast dynamic response of the coronary system (short $t_{50}$ value) may lead to unstable flow regulation, which in turn may be associated with imbalanced flow distribution or vasospasm. There is evidence that coronary vasospasm plays an important role in the etiology of perioperative myocardial ischemia, developing in patients with CAD undergoing surgery [20,21]. These ischemic episodes are significantly more prevalent in the period before induction of anesthesia (i.e. in the awake situation) than during deep surgical anesthesia [22-28].

Measuring the response time of the human coronary system before and during anesthesia in the same patients is a first step in understanding the potential role of the dynamics of coronary flow adaptation in the pathophysiology of coronary perfusion in humans. Therefore, the present study was designed to measure the dynamic characteristics of coronary flow adaptation in response to stepwise changes in HR in awake and anesthetized patients with CAD, scheduled for coronary artery surgery.
2. Methods and materials

2.1 Patients
Eleven patients with stable CAD, scheduled for elective coronary artery surgery, gave informed consent to participate in this study which had institutional approval. Excluded from the study were patients with the following conditions: left ventricular end diastolic pressure > 18 mmHg, left ventricular hypertrophy (assessed by electrocardiographic or echocardiographic criteria), ejection fraction < 45 %, atrioventricular conduction defects, left main coronary stenosis or unstable angina. Patients undergoing additional surgical procedures e.g. valve replacement or aneurysmectomy were also excluded.

2.2 Instrumentation
On arrival in the operating room ECG leads were connected. Leads II, III and V₅ were continuously monitored (HP Merlin System, Hewlett-Packard, Böblingen, Germany). A wide bore peripheral infusion and a 20-gauge radial artery canula were inserted under local analgesia.

In awake patients, a triple lumen pulmonary artery catheter (Baxter Health Care Corporation, Irvine, California, USA) and a coronary sinus thermodilution catheter (Wilton-Webster Laboratories, Altadena, California, USA) were introduced via the left subclavian vein. The coronary sinus catheter was advanced into the coronary sinus using image intensification fluoroscopy and injection of contrast medium, so that the external thermistor lay 1.5-2 cm from the ostium and that there was no major sidebranching vein in the vicinity. The coronary sinus catheter was connected to a Wheatstone bridge (Wilton-Webster Laboratories, Altadena, California, USA). Coronary sinus thermodilution signals were recorded with a multi-channel amplifier/recorder system. Catheter calibration factors provided by the manufacturer were used. The absence of right atrial admixture in coronary sinus blood was checked by injection of cold saline in the right atrium, while coronary sinus temperature curves were recorded simultaneously [29,30]. Under fluoroscopy, pacing (via coronary sinus catheter) was used during 10-30 sec to ascertain the stability of the position of the tip of the coronary sinus catheter in relation to the surrounding anatomical structures and fluoroscopic landmarks. If the stability of the catheter could not be guaranteed at that time, the experiment was discontinued prematurely. In addition, the electrical threshold for pacing was determined. For the measurement of coronary sinus blood flow (CSBF) normal saline at room temperature was used as indicator and infused into the coronary sinus at a rate of 45 ml·min⁻¹ via a Mark IV infusion pump (Medrad Technology for people, Pittsburgh, Pennsylvania, USA) [31]. Infusion rates were verified by timed volume collection and flow calculations reflected the indicator infusion rate that was used.

2.3 Anesthesia technique
Calcium channel blockers and long acting nitrates were given until the evening before surgery. β-adrenoreceptor blocking agents were continued until the morning of surgery. Lorazepam 4-5 mg was given for premedication 2 hours before surgery.
In the operating room, while the patients breathed oxygen, pancuronium bromide 2 mg was given, followed by fentanyl 100 μg·kg⁻¹, injected over 5 minutes. When the patient became unresponsive to commands an additional dose of pancuronium 6 mg was given and ventilation assisted and then controlled manually. After intubation of the trachea the lungs were ventilated with air/oxygen (FIO₂ = 0.5). Ventilation was adjusted to maintain the end-tidal CO₂ concentration between 4.4.5 %. In the first 15 minutes following induction of anesthesia, 250-500 ml of gelofusine (Vifor Medical SA, Crisier, Switzerland) was infused to maintain a stable hemodynamic situation after induction of anesthesia. Gelofusine is a gelatin solution, containing per 500 ml: modified gelatin 20 g; Na⁺ 77 mmol; Cl⁻ 63 mmol; pH 7.1-7.7; osmolality 279 mOsm/l.

2.4 Measurements
After adequate instrumentation and a resting period of 20 minutes the following measurements were performed in awake and anesthetized patients (figure 6.1, flowchart).

At the beginning of each series of measurements a complete set of hemodynamic measurements profile including pulmonary capillary wedge pressure (PCWP) and single bolus thermodilution cardiac output was obtained, using injectate at room temperature. Cardiac output (CO) is calculated as the average of at least three
measurements and reported as cardiac index (CI). Blood samples from the radial artery and coronary sinus were drawn to determine plasma hemoglobin (Hb) concentration, oxygen partial pressure (pO₂), hemoglobin O₂ saturation (SatO₂) and lactate concentration.

After completion of the intermittent measurements, continuous recording of CSBF, arterial blood pressure (ABP), right atrial pressure (RAP), pulmonary artery pressure (PAP) and electrocardiographic lead II was started at a sampling rate of 80 Hz and stored on floppy disk. When a steady state in coronary sinus thermodilution signal was obtained after 10-15 seconds of registration, HR was abruptly increased by 25 beats per minute by pacing via the coronary sinus catheter. After a recording period of 70 seconds indicator infusion was discontinued. Pacing was continued at the same rate. Immediately following the completion of the continuous recordings, all intermittent measurements and blood sampling were repeated.

During pacing, continuous measurements were resumed. After a steady state in CSBF-signal was obtained (10-15 sec) pacing was stopped. Recording of thermodilution signals, blood pressures and ECG continued for a total duration of 70 seconds. A final series of hemodynamic measurements and blood sampling completed the measuring protocol in the awake patient. Then, anesthesia was induced following the technique described above. Twenty minutes after induction of anesthesia and tracheal intubation, the complete protocol was repeated.

Below, the increase and decrease in HR will be referred to as HR step up and HR step down, respectively.

2.5 Laboratory analysis and calculations
SatO₂ was measured by an OSM-II hemoxyimeter (Radiometer, Copenhagen, Denmark) and pO₂ by an ABL-III (Radiometer, Copenhagen, Denmark). Lactate concentrations were measured using standard enzymatic techniques [32].

Calculated hemodynamic parameters were obtained from measured hemodynamic signals using standard formulae:

\[ CVR = \frac{(ABP - RAP)}{CSBF} \text{[mmHg/ml/min]} \]
\[ CI = \frac{CO}{BSA} \text{[l/min/m²]} \]

Where: CVR indicates coronary vascular resistance in steady state; ABP, mean arterial blood pressure; RAP, mean right atrial pressure; CSBF, coronary sinus blood flow; CI, cardiac index; CO, cardiac output; BSA, body surface area;

Myocardial metabolic indices were calculated according to standard formulae:

\[ cO₂ = (Hb \cdot SatO₂ + 0.00136 \cdot pO₂) \cdot 2.24 \text{ [ml O₂/dl]} \]
\[ MVO₂ = CSBF \cdot (cO₂_{\text{art}} - CO₂_{\text{muc}}) / 100 \text{ [ml O₂/min]} \]
\[ MLE = 100 \cdot (\text{lactate}_{\text{art}} - \text{lactate}_{\text{muc}}) / \text{lactate}_{\text{muc}} \text{ [%]} \]
Figure 6.2: Method of calculating t_{50}-values. A high-order polynomial was fitted to the normalized coronary resistance index (CRI), starting 2 s after the intervention (increase in heart rate). The value of the polynomial at 2 s after the HR step was used as begin value, whereas the average of the last 10 seconds of CRI was used as end value. The t_{50} value was calculated as the time after the HR step at which the polynomial reached 50% of the difference between begin and end value.

Where: cO_2 indicates oxygen content; Hb, plasma hemoglobin concentration; SatO_2, hemoglobin oxygen saturation; cO_2_{art} - cO_2_{cs}, difference between arterial and coronary sinus oxygen content; MVO_2, myocardial O_2 consumption; MLE, myocardial lactate extraction percentage; lactate_{art}, lactate concentration in arterial blood; lactate_{cs}, lactate concentration in coronary sinus blood.

2.6 Data analysis
The response of the coronary vascular tree to pacing induced stepwise changes in heart rate was analyzed as described by Dankelman et al. [8]. ABP, RAP and CSBF were averaged per beat. The coronary resistance index (CRI) was then calculated as the quotient of beat-averaged ABP-RAP and CSBF. The CRI is identical to CVR in steady state. Under conditions in which flow and/or pressure vary so slowly that capacitance effects can be ignored CRI reflects CVR. During fast dynamic changes in driving pressure or CSBF, CRI does not reflect CVR [7,33]. For this reason the first 2 seconds after a heart rate step were not included in the analysis of CRI, since after 2 seconds the major capacitive effects are complete.

The rate of the coronary adaptation was quantitated by a t_{50}-value, which was defined as the time in seconds after a HR-step at which the change in CRI had reached 50% of its total change. Using a signal analysis program (386-Matlab,
version 3.5j (1991), The MathWorks Inc., Natick, Massachusetts, USA), this value was calculated by fitting a high order polynomial to a part of the signal over a period of at least 10 seconds around the 50 % value of the coronary resistance index. (figure 6.2) 

To compare the time course of the response of the CRI to the different interventions, the CRI was normalized. The normalized index was calculated by averaging CRI over 8 sec prior to the HR step, yielding CRIo. The normalized coronary resistance index is then given by:

$$\text{CRI}_o(t) = \frac{\text{CRI}(t)}{\text{CRI}_o}$$

The normalized response of the CRI starts at unity and as a result of the coronary regulation process finally decreases (HR step up) or increases (HR step down).

2.7 Statistical analysis

Data were analyzed using paired standard t-tests. A value of p < 0.05 was considered significant. Results are reported as mean ± SD or as percentage change ± SD where applicable.

3. Results

3.1 Characteristics of the patients

Patients characteristics and pre-operative chronic medication are shown in table 6.1. The patients were comparable with respect to age, weight, and length. Although five patients had suffered a previous myocardial infarction and three had (treated) hypertension, there was no evidence of either impaired left ventricular function and dilation or left ventricular hypertrophy. One patient (#4) was not using chronic β-adrenoreceptor blockers. Patients 3 and 5 were not using calcium entry blockers. Patients 2, 6, 9 and 10 were not using long acting nitrates preoperatively.

3.2 Hemodynamic and metabolic characteristics

Systemic and coronary hemodynamic variables and myocardial metabolic data are listed in table 6.2. Hemodynamic results obtained in both the awake and anesthetized condition are reported at baseline, after onset of pacing (HR up), before and after discontinuation of pacing (HR down).

The stepwise changes in HR tended to be larger during anesthesia, because after induction of anesthesia, HR decreased from 60 to 55 beats per minute, while the rate of pacing that was used in the awake situation was not changed. All HR steps resulted in a change in ABP in the direction of the HR step and during anesthesia these changes in ABP were significantly larger, compared to the awake state. Awake, a HR step up resulted in a blood pressure increase of 4 mmHg, while during anesthesia this pressure increase was 14 mmHg. Similarly, a HR step down resulted in a blood pressure decrease of 3 mmHg in the awake state, and a blood pressure decrease of 15 mmHg in the anesthetized state. Compared to the awake situation, ABP decreased in all patients after induction of anesthesia.
**Table 6.1:** Patient characteristics and clinical data

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Length (cm)</th>
<th>Weight (kg)</th>
<th>Extent of CAD</th>
<th>Prior MI</th>
<th>Hypertension</th>
<th>Chronic Preoperative Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>M</td>
<td>172</td>
<td>85</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>no</td>
<td>LAN, β-blocker, CEB</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>157</td>
<td>58</td>
<td>RCA, LAD</td>
<td>yes</td>
<td>yes</td>
<td>β-blocker, CEB, ACE inhibitor</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>175</td>
<td>73</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>no</td>
<td>LAN, β-blocker</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>176</td>
<td>70</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>yes</td>
<td>LAN, CEB</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>M</td>
<td>171</td>
<td>94</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>no</td>
<td>LAN, β-blocker</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>M</td>
<td>182</td>
<td>78</td>
<td>RCA, LAD, LCX</td>
<td>yes</td>
<td>no</td>
<td>β-blocker, CEB</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>M</td>
<td>185</td>
<td>86</td>
<td>RCA, LAD</td>
<td>yes</td>
<td>no</td>
<td>LAN, β-blocker, CEB</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>M</td>
<td>174</td>
<td>70</td>
<td>LAD, LCX</td>
<td>yes</td>
<td>no</td>
<td>β-blocker, CEB</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>M</td>
<td>172</td>
<td>80</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>no</td>
<td>β-blocker, CEB</td>
</tr>
<tr>
<td>10</td>
<td>54</td>
<td>M</td>
<td>172</td>
<td>97</td>
<td>RCA, LAD, LCX</td>
<td>yes</td>
<td>yes</td>
<td>LAN, β-blocker, CEB</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>M</td>
<td>180</td>
<td>86</td>
<td>RCA, LAD, LCX</td>
<td>no</td>
<td>no</td>
<td>LAN, β-blocker, CEB</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery. MI indicates myocardial infarction. LAN indicates long acting nitrate and CEB, calcium entry blocker.
### Table 6.2:
Hemodynamic and metabolic data

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th></th>
<th></th>
<th>Anesthesia</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR increase</td>
<td>HR decrease</td>
<td>HR increase</td>
<td>HR decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>before</td>
<td>after</td>
<td>before</td>
<td>after</td>
<td>before</td>
<td>after</td>
</tr>
<tr>
<td>HR (1/min)</td>
<td>60±8</td>
<td>86±6*</td>
<td>85±7</td>
<td>59±8*</td>
<td>55±6</td>
<td>85±9*</td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td>103±21</td>
<td>107±22*</td>
<td>109±23</td>
<td>106±22*</td>
<td>78±16*</td>
<td>92±18*</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>6±4</td>
<td>5±4</td>
<td>5±5</td>
<td>6±4</td>
<td>8±4</td>
<td>7±4</td>
</tr>
<tr>
<td>PAP (mmHg)</td>
<td>22±5</td>
<td>25±5*</td>
<td>24±5</td>
<td>23±5</td>
<td>20±5</td>
<td>23±5*</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>11±4</td>
<td>11±6</td>
<td>11±6</td>
<td>11±5</td>
<td>11±3</td>
<td>11±3</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.5±0.7</td>
<td>3.3±0.7*</td>
<td>3.3±0.7</td>
<td>2.7±0.6*</td>
<td>2.2±0.5</td>
<td>3.0±0.7*</td>
</tr>
<tr>
<td>CSBF (ml/min)</td>
<td>109±27</td>
<td>159±43*</td>
<td>156±34</td>
<td>109±27*</td>
<td>91±40*</td>
<td>119±43*</td>
</tr>
<tr>
<td>CVR (mmHg/ml/min)</td>
<td>0.96±0.38</td>
<td>0.71±0.30*</td>
<td>0.72±0.28</td>
<td>0.99±0.38*</td>
<td>0.80±0.35</td>
<td>0.70±0.26*</td>
</tr>
<tr>
<td>Cao₂ (ml O₂/dl)</td>
<td>17.9±2.3</td>
<td>17.9±2.3</td>
<td>17.9±2.3</td>
<td>17.8±2.4</td>
<td>19.1±2.3*</td>
<td>19.0±2.3</td>
</tr>
<tr>
<td>CaO₂ (ml O₂/dl)</td>
<td>5.9±1.4</td>
<td>6.2±1.4</td>
<td>6.2±1.4</td>
<td>6.1±1.3</td>
<td>7.3±1.4*</td>
<td>7.1±1.2</td>
</tr>
<tr>
<td>SatO₂ (%)</td>
<td>98±2</td>
<td>97±3</td>
<td>97±3</td>
<td>97±3</td>
<td>100*</td>
<td>100</td>
</tr>
<tr>
<td>SatO₂ (%)</td>
<td>33±7</td>
<td>34±7</td>
<td>34±7</td>
<td>34±7</td>
<td>40±7*</td>
<td>40±6</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>119±33</td>
<td>118±40</td>
<td>118±40</td>
<td>112±40</td>
<td>349±86*</td>
<td>324±119</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>22±2</td>
<td>22±2</td>
<td>22±2</td>
<td>22±2</td>
<td>26±3*</td>
<td>23±3</td>
</tr>
<tr>
<td>MVO₂ (ml O₂/min)</td>
<td>12.8±4.3</td>
<td>18.1±7.1*</td>
<td>18.1±7.1</td>
<td>12.5±4.6*</td>
<td>11.5±5.1*</td>
<td>16.9±8.0*</td>
</tr>
<tr>
<td>MO₂E (%)</td>
<td>67±7</td>
<td>65±7</td>
<td>65±7</td>
<td>66±6</td>
<td>61±6*</td>
<td>62±6</td>
</tr>
<tr>
<td>MLE (%)</td>
<td>47±21</td>
<td>40±10</td>
<td>40±10</td>
<td>36±17</td>
<td>46±12</td>
<td>38±10</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n = 11. Values of heart rate (HR), mean arterial blood pressure (ABP), mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), coronary sinus blood flow (CSBF), coronary vascular resistance (CVR), arterial and coronary sinus oxygen content (Cao₂ and CaO₂), arterial and coronary sinus hemoglobin oxygen saturation (SatO₂ and SatO₂), arterial and coronary sinus oxygen partial pressure (pO₂ and pO₂), myocardial oxygen consumption (MVO₂), myocardial oxygen extraction (MO₂E) and myocardial lactate extraction (MLE), before and after HR-steps up and down, in the awake and anesthetized state. *p < 0.05 vs. value before HR-step; 'p<0.05 vs. corresponding value awake. **p<0.05 vs. corresponding change, awake.
ANESTHESIA AND RATE OF CORONARY FLOW CONTROL

After a HR step up, mean CSBF increased by 46% in the awake state, and also by 46% in the anesthetized state and after a HR step down mean CSBF decreased by 29% and 32%, respectively. Compared to the awake situation, CSBF decreased in all patients after induction of anesthesia. CVR decreased significantly after a HR step up, remained at the same level during pacing and increased after a HR step down. These changes were in the same order of magnitude in both the awake and anesthetized condition (p >0.39).

Before a HR step up, during a pacing period (with CSBF at steady state), and after a HR step down (figure 6.1), coronary sinus oxygen tension ($p_{cs}O_2$), MVO$_2$ and MLE could be calculated. In the awake and anesthetized situation, $p_{cs}O_2$ did not change in response to HR changes, although $p_{cs}O_2$ increased 3-4 mmHg (p<0.05) after induction of anesthesia.

MVO$_2$ increased significantly during pacing and this change in MVO$_2$ was similar in both the awake and anesthetized state. However, at baseline before the HR step up and step down, the level of MVO$_2$ was 1.3 ml O$_2$·min$^{-1}$ and 1.2 ml O$_2$·min$^{-1}$ less (p<0.05) during anesthesia than in the awake state.

MLE did not change during pacing and after induction of anesthesia and remained positive in all our patients, during all interventions. Furthermore, we did not observe electrocardiographic signs of myocardial ischemia in any patient at any time during the entire study period.

There was no significant change in arterial-venous oxygen content difference between the awake and anesthetized state. The arterial oxygen content increased from 8.0 ± 0.9 mmolO$_2$·l$^{-1}$ awake to 8.5 ± 1.0 mmolO$_2$·l$^{-1}$ during anesthesia (p<0.05), while arterial oxygen supply decreased, due to a decreased coronary flow. The myocardial oxygen extraction percentage (MO$_2$E) did not change in response to the HR steps, but decreased after induction of anesthesia, due to the increase in arterial oxygen content.

3.3 Dynamic characteristics of coronary control

Typical results obtained by increasing HR, are shown in figure 6.3. In the awake state, CSBF increased to a new steady state level, indicating coronary dilation. In the anesthetized state this vasodilating response became slower, as is clear from the normalized response of coronary resistance index.

The response rates as induced by the different interventions of all individual patients were quantified by t$_{50}$-values, which are shown in table 6.3. Fentanyl anesthesia clearly reduced the rate of adaptation of the coronary resistance index. In the awake situation, t$_{50}$-values of the dilating and constricting responses, induced by an increase and decrease in heart rate were 5.0 ± 2.1 (SD) sec and 5.7 ± 1.2 sec, respectively. During anesthesia the rate of change of coronary flow adaptation was significantly decelerated with t$_{50}$-values of 10.2 ± 2.1 sec after a heart rate step up and 9.8 ± 2.1 sec after a heart rate step down. The rate of the vasoconstricting response to a decrease in HR and the vasodilating response to an increase in HR were similar and this applied to both the awake and anesthetized state.
Figure 6.3: Recordings showing the response of arterial blood pressure (ABP), right atrial pressure (RAP), coronary sinus blood flow (CSBF) and normalized coronary resistance index (CRI_n) to an increase in heart rate at t=0 s, awake (left) and during anesthesia (right).

4. Discussion

The aim of the present study was to measure the rate of change of coronary blood flow in response to HR steps in awake and anesthetized patients with CAD. It was demonstrated that in awake patients the dynamic process of adaptation of coronary flow in response to stepwise changes in HR and MVO_2 takes place in 5.2 ± 1.6 seconds. Fentanyl/pancuronium anesthesia significantly (p<0.001) delayed this adaptation to 10.0 ± 1.7 seconds.

4.1 Techniques

In the present study the coronary venous thermodilution technique was chosen, because this technique has been used successfully in hundreds of patients undergoing both cardiac and non-cardiac surgery [34-36]. There are a number of limitations to its use that are related both to the physiology and anatomy of the coronary venous drainage and to the thermodilution technique itself [29,30,37-42]. The major anatomical problem is formed by the existence of extensive cardiac venous intercommunications, resulting in drainage of left anterior descending arterial blood through routes other than the great cardiac vein and the coronary sinus [38,40,42]. This may result in an underestimation of coronary blood flow. Since, in the present study we focused on the dynamic adaptation of flow in response to HR steps and
**Table 6.3:**  
Rate of coronary regulation in response to changes in heart rate

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>HR up</th>
<th>HR down</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>1</td>
<td>6.9</td>
<td>12.9</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>10.6</td>
</tr>
<tr>
<td>3</td>
<td>9.0</td>
<td>7.7</td>
</tr>
<tr>
<td>4</td>
<td>2.6</td>
<td>7.9</td>
</tr>
<tr>
<td>5</td>
<td>4.2</td>
<td>8.7</td>
</tr>
<tr>
<td>6</td>
<td>6.3</td>
<td>12.9</td>
</tr>
<tr>
<td>7</td>
<td>7.0</td>
<td>13.1</td>
</tr>
<tr>
<td>8</td>
<td>2.9</td>
<td>11.0</td>
</tr>
<tr>
<td>9</td>
<td>3.5</td>
<td>8.2</td>
</tr>
<tr>
<td>10</td>
<td>4.8</td>
<td>11.0</td>
</tr>
<tr>
<td>11</td>
<td>3.2</td>
<td>8.4</td>
</tr>
<tr>
<td>mean (SD)</td>
<td>5.0 ± 2.1</td>
<td>10.2 ± 2.1</td>
</tr>
<tr>
<td><em>p</em></td>
<td>0.0001</td>
<td>0.00003</td>
</tr>
</tbody>
</table>

HR indicates heart rate; *t*\(_{50}\)-values, time in seconds after the heart rate step at which the coronary resistance index had changed 50% of its total change.

Not on absolute blood flow values, these venous intercommunications and the potential underestimation of the absolute coronary blood flow are probably of no importance for this study.

Movement of the catheter in the coronary sinus may induce an important change in measured flow, presumably because of the varying contribution of venous tributaries [37,41]. Both pacing and changes in heart size following the induction of anesthesia are factors that may have influenced the position of the coronary sinus catheter. The effect of pacing on the stability of the tip of the coronary sinus catheter was ascertained and we have no indication from the thermodilution recordings that shifts in catheter position after a HR step occurred.

Movement of the catheter following induction of anesthesia could have been partly responsible for the absolute reduction in CSBF. However, this does not affect the measurement of the rate of the coronary responses after a HR step. For the actual calculation of the *t*\(_{50}\)-values, the rate of change of CVR in response to a HR step was used and therefore, absolute values of CSBF are of minor importance. Furthermore, absolute CVR was similar before each series of measurements, both awake and during anesthesia.

### 4.2 Possible influence of the extent of coronary artery disease on the rate of change of coronary flow

Comparison of our findings with healthy human data is not possible, since, to the best of our knowledge, data describing the rate of adaptation of coronary flow in
humans have not been reported. Table 6.4 shows the previously reported $t_{50}$ values (recalculated) of the coronary arterial systems of dogs and goats and the $t_{50}$ values obtained in patients with CAD in the present study. Therefore all $t_{50}$ values were calculated using the same analysis technique as described in the methodology section. It appears that the rate of coronary adaptation in anesthetized humans is similar to the rate of coronary adaptation in anesthetized goats. In dogs and goats, using a coronary perfusion system, the effects of both constant pressure (CP) and constant flow (CF) perfusion could be studied. It was shown that the $t_{50}$ values of the coronary system were $\pm 50\%$ larger at CF perfusion than at CP perfusion [6,7]. CF perfusion was induced by placing a clamp on the perfusion catheter which may resemble the effect of a stenosis. All our patients had severe coronary lesions, although not left main coronary stenosis. Hence, in case the coronary stenoses in our patients had affected the results of the present study, the reported $t_{50}$ values are probably larger than the values that we would have found in patients without coronary stenoses, in both the awake and anesthetized state.

4.3 Rate of change of myocardial oxygen consumption and changes in coronary hemodynamics

A number of factors may have influenced the rate of change of the coronary vascular wall after induction of anesthesia. These factors include: the rate of change of MVO$_2$, the reduction in coronary perfusion pressure and CSBF and the increase in coronary venous pO$_2$.

In our clinical experimental setup we could not measure oxygen consumption of the myocardium continuously. Comparing the course of the rate pressure product (RPP) as a measure of MVO$_2$ after a sudden change in HR in the awake and anesthetized state, the change in RPP after a HR step was always instant. This suggests an instant and similar change in MVO$_2$ [43,44], both awake and during anesthesia. It therefore seems unlikely that the rate of change of MVO$_2$ played a role in the observed deceleration of coronary responses following induction of anesthesia.

The reductions in CSBF and ABP and thus coronary perfusion pressure, associated with induction of anesthesia are factors that also must be considered as a potential explanation for the reduction in the rate of change in CRI. Animal experiments have yielded evidence that the rate of coronary adaptation is relatively independent of the level of coronary blood flow and that a reduction in coronary perfusion pressure results in an increase and not a decrease in the rate of change of coronary resistance [6]. That implies that the in our study reported $t_{50}$-values during anesthesia might have been even longer if ABP would have remained unchanged following induction of anesthesia. Furthermore, it is unlikely that differences in CVR and HR at baseline have affected the results of our study [45]. CVR's at baseline, in both the awake and anesthetized state, were similar. Although there was a significant reduction in HR following induction of anesthesia (60 beats·min$^{-1}$ awake versus 55 beats·min$^{-1}$ under anesthesia), this difference at baseline is within such a narrow range, that it can hardly have played a role.
Table 6.4:
Rate of coronary regulation in response to changes in heart rate

<table>
<thead>
<tr>
<th></th>
<th>Anesthesia</th>
<th></th>
<th>Awake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CP</td>
<td>CF</td>
<td>CP</td>
</tr>
<tr>
<td></td>
<td>HR up</td>
<td>HR down</td>
<td>HR up</td>
</tr>
<tr>
<td>dogs</td>
<td>4.7 ± 0.4</td>
<td>5.1 ± 0.3</td>
<td>7.9 ± 0.6</td>
</tr>
<tr>
<td>goats</td>
<td>9.4 ± 1.1</td>
<td>11.1 ± 0.9</td>
<td>14.6 ± 1.4</td>
</tr>
<tr>
<td>patients</td>
<td>10.2 ± 0.6</td>
<td>9.8 ± 0.6</td>
<td>5.0 ± 0.7</td>
</tr>
</tbody>
</table>

Mean ± S.E.M. t50-values indicate time in seconds after change in heart rate at which the coronary resistance index has changed 50 % of its total change; CP, constant pressure perfusion; CF, constant flow perfusion; HR, heart rate; CAD, coronary artery disease.

Although coronary perfusion pressure could not be controlled with an extra corporeal perfusion system, patient data are listed under constant pressure perfusion because constant pressure perfusion resembles the situation with normal aortic perfusion, and not under constant flow perfusion since coronary blood flow was not constant.

Finally, the increase in coronary venous pO2 following induction of anesthesia may have influenced the rate of coronary flow adjustment. Dole et al. demonstrated in anesthetized dogs that the strength of coronary autoregulation and its dynamic behavior is influenced by the level of coronary venous pO2 [46]. They concluded that there is a marked attenuation of autoregulation at venous pO2 levels above 30 mmHg. In our study the venous pO2 was below the threshold level of 30 mmHg at all time, although there was a small, but significant, change in coronary venous pO2 between the awake and anesthetized state.

Thus, there are no myocardial metabolic or coronary hemodynamic factors that can clearly explain the reported increase in the rate of coronary flow adjustment following the induction of anesthesia.

4.4 Pharmacological effects directly or indirectly induced by anesthetic agents

In the present study, fentanyl and pancuronium bromide were the only pharmacological agents used for the induction and maintenance of anesthesia and muscle relaxation. Unfortunately, little is known about the impact of these agents on the multifactorial process of coronary flow regulation. Therefore, it is not possible to develop a specific pharmacological mechanism explaining the effect of anesthesia on the dynamic response of human coronary flow regulation.

It is known from animal models that the rate of change of coronary resistance can be influenced by drugs [8]. It has been demonstrated in goats with normal coronary arteries anesthetized with fentanyl, that glibenclamide, an antidiabetic drug with blocking effects on ATP dependent potassium channels in vascular smooth muscle tissue, can reduce the rate of change of coronary resistance by a factor of 4, without changing the steady state relations of coronary hemodynamics [8]. Glibenclamide has been shown to have an inhibiting effect on membrane hyperpolarization of the
vascular smooth muscle cell [47]. In contrast, fentanyl is associated with membrane hyperpolarization of neuronal cells via potentiation of the K+ channel current [48,49]. However, it is not known if there is a direct effect of fentanyl on myocardial or coronary vascular smooth muscle membranes. An indirect effect of fentanyl, via reduction of circulating catecholamine concentrations and sympathetic activity [50-53], appears to be an unlikely factor to explain our findings, because all patients (except for patient #4) were adequately β-blocked both awake and during anesthesia. However, the involvement of coronary α-receptor constrictor mechanisms (in the presence of high levels of circulating catecholamines) competing with metabolic vasodilation can not be excluded [54].

Pancuronium bromide is a steroid based non depolarizing muscle relaxant with additional blocking effects on muscarinic receptors [11,55]. Muscarinic receptors are involved in the local release of endothelium derived relaxing factor from endothelium [56-58]. This substance plays a role in the local regulation of coronary blood flow, via an effect on flow dependent dilation [59-61]. Theoretically, this mechanism might affect our findings.

4.5 Clinical implications of the present findings
The clinical implications of our findings remain mostly speculative, since the present study was not designed to address a specific clinical problem and because the concept of dynamic coronary flow adaptation has never been described before as a parameter of coronary function in humans. From the results of our study one can not conclude that the awake coronary responses were “normal” and the responses obtained under anesthesia were slow or the opposite, i.e. that the responses in awake patients with CAD were fast and the responses under anesthesia were “normal”. Thus far, no studies describing the dynamics of coronary flow in humans with normal coronary arteries have been reported and thus we do not know the normal tso value of coronary flow adaptation in healthy humans.

The higher rate of flow adjustment found during our measurements in awake patients might imply that the coronary system can follow a high frequency of stimulation and therefore, has little damping and a high probability of oscillation [19]. Oscillation may result in unstable flow regulation. Although highly speculative, it is possible that unstable flow regulation in the presence of multiple rapid changes in HR and MVO₂ may lead to an imbalance in flow distribution or coronary spasm and subsequently myocardial ischemia.

Finally, the results of the present study suggest the existence of a specific mechanism for controlling the dynamics of coronary resistance. Since fentanyl in combination with pancuronium can influence this mechanism, it may be possible to identify or develop other compounds with a specific effect on the rate of coronary flow adjustment.

5. Conclusions
Fentanyl/pancuronium anesthesia did not change steady state regulation of coronary blood flow in patients with CAD. However, our preliminary findings suggest that in
these patients the rate of change of coronary flow adjustment is reduced by this anesthetic technique. A further qualification of our findings in a larger number of patients is warranted.

6. References


Anesthesia and rate of coronary flow control


