Cardiac-coronary interactions in humans: Mechanistic insights from wave intensity analysis
Rolandi, Cristina

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Chapter 3

Coronary Wave Intensity during the Valsalva Manoeuvre in Humans Reflects Altered Intramural Vessel Compression Responsible for Extravascular Resistance

M. Cristina Rolandi, Froukje Nolte, Tim P. van de Hoef, Maurice Remmelink, Jan Baan Jr, Jan J. Piek, Jos A.E. Spaan, Maria Siebes

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ABSTRACT

Our aim was to investigate the effect of altered coronary-cardiac interaction during the Valsalva manoeuvre (VM) on coronary wave intensity and the response of coronary microvascular resistance (MR).

In 13 patients, left ventricular (P\textsubscript{LV}) and aortic pressure (P\textsubscript{a}) were measured during catheterization, together with intracoronary pressure (P\textsubscript{d}) and blood flow velocity (U) via a dual-sensor guide wire advanced into an angiographically normal coronary artery. Signals were analyzed for the following phases of VM: baseline (B1), onset of strain (S1), sustained strain (S2), onset of release (R1), maximal response during recovery (R2), and baseline after VM.

The immediate effects of VM were most evident from diastolic P\textsubscript{LV} (LVDP), which increased from 11.0±2.3 to 36.4±2.7 mmHg between B1 and S1 and fell from 28.3±3.4 to 8.3±1.9 mmHg between S2 and R1. Wave intensities (WI) and rate pressure product (RPP) were only minimally affected at these transient phases, but WI decreased by about 50% and RPP by 38% from S1 to S2, together with a 30% depression of LVdP/dt. All signals were restored to baseline values during the recovery. U did not vary significantly throughout the VM. Despite the depressed cardiac performance, microvascular resistance, calculated with LVDP as backpressure, decreased by 31% from B1 to S2, which was unexpected since a metabolically-induced vasoconstriction was expected.

Since coronary U remained essentially constant despite the marked reduction in oxygen consumption, microvascular vasoconstriction must have been compensated by a decrease in the contraction-mediated impediment on coronary blood flow, as confirmed by the reduced coronary wave energies.
INTRODUCTION

Despite decades of studies on the interaction between cardiac contraction and coronary blood flow, mechanisms underlying coronary perfusion and the coronary pressure and flow waveforms are still not satisfactorily understood. Moreover, it is recognised that theoretical models of coronary physiology should be validated by human data. Recently, a time domain method has been developed for investigating hemodynamic waveforms in terms of coincident successive wavefronts that cause an incremental change in pressure or velocity as they pass the measurement site. This wave intensity analysis enables separation of the local net waveform into forward and backward travelling components for pressure, velocity and net wave intensity signals [1]. Amplitude and direction can be distinguished from a single set of measurements at an accessible site remote from where the waves originated. In the coronary circulation, wave intensity can differentiate between forward waves arriving via the aorta and backward waves originating in the microcirculation due to cardiac contraction and relaxation [2-3].

Hence, wave intensity is a powerful tool to investigate cardiac-coronary interaction and it is increasingly being used to interpret clinical data, e.g. regarding the effects of myocardial or aortic valve disease [4-5] or the impact of intra-aortic balloon inflation on coronary flow [6].

Apart from its physiological relevance, understanding of the interaction between cardiac contraction and the coronary circulation has also clinical implications for the functional assessment of coronary artery disease. Several physiological indices are being used to assess the impact of a coronary stenosis on myocardial perfusion [7-9] and new ones are being developed [10], which not always possess adequate support from underlying physiological models [11]. Rather than using simple mean indices based on lumped parameter models, a different approach is undertaken by others to develop more realistic multi-scale, multi-physics models to aid in personalization of clinical diagnosis [12-13]. Such coronary models require a test set of human data for validation, describing the response of the coronary system to variations in hemodynamic parameters relevant to regulatory responses and changes in mechanical function of the heart.

In this study we used the Valsalva manoeuvre (VM) to investigate in the human coronary circulation the interaction between hemodynamic and mechanical factors responsible for the morphology of the coronary flow velocity and pressure waveforms and derived signals such as wave intensity. The VM generates rapid changes in blood pressures at the onset and release of increased intrathoracic pressure, but also contains periods of more or less stable circumstances where the adaptation of the coronary circulation over time can be followed [14-15].

The hypothesis of this study is that the energy of coronary waves is poorly related to the mean epicardial flow velocity when cardiac function is not stable and that the beat-averaged coronary resistance not only depends on control of tone in the resistance vessels, but also on extravascular compression.
METHODS

Ethical approval
All study procedures were approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam. Written informed consent was obtained from all subjects, and the studies conformed to the Declaration of Helsinki.

Subject characteristics
Thirteen patients with stable angina pectoris scheduled for elective percutaneous coronary intervention were included in the study. Inclusion criteria were a single de novo stenosis in one coronary artery and one angiographically normal reference vessel. Exclusion criteria were subtotal or serial lesions, significant left main coronary artery stenosis, severe aortic valve disease, recent myocardial infarction (<6 weeks), prior cardiac surgery, hypertrophic cardiomyopathy or severe heart failure.

Experimental procedures
All anti-anginal and antiplatelet medication was continued as clinically indicated. Cardiac catheterization was performed using femoral approach. All patients received a bolus of heparin (5000 IU) and nitroglycerin (0.1 mg, intracoronary) at the beginning of the procedure. Left ventricular pressure (P_{LV}) was measured via a 5-F pigtail catheter. Aortic pressure (P_{a}) was obtained at the coronary ostium via a 5F or 6F guiding catheter. Distal intracoronary pressure (P_{d}) and blood flow velocity (U) were measured via a novel 0.014-in dual-sensor guidewire (Combowire®, Volcano Corp., San Diego, CA) equipped with both a Doppler sensor and a pressure sensor at the tip. The wire was advanced into the angiographically normal reference vessel and manipulated until an optimal and stable velocity signal was obtained. All hemodynamic data reported here were acquired without pharmacological vasodilation prior to treatment of the target lesion. After baseline recordings, the patient performed at least one VM by exhaling against the closed glottis. The hemodynamic signals and the ECG were processed with the associated instrument console and digitized at a sampling frequency of 200 Hz for off-line analysis.

Data Analysis
Quantitative coronary angiography (QAngio XA v. 7.2, Medis Medical Imaging Systems, Leiden, The Netherlands) was performed to obtain the diameter reduction of the study vessel. From the continuous recordings, at least three consecutive cardiac cycles were selected at baseline before (B1) and after (B2) the VM, and 1-3 representative cycles during the characteristic four phases of the manoeuvre: at the beginning of strain (S1), at maximum strain (S2), at sudden release (R1) and during the early recovery phase (R2). These hemodynamic data were processed using a custom-made program (Delphi v. 2010, Embarcadero, CA, USA). Time derivatives were obtained after smoothing the raw signals with a Savitzky-Golay filter [16] and then ensemble averaged over the beats of interest. The maximum and minimum derivative of P_{LV} (LVdP/dt) were derived as a measure of the speed
of contraction and relaxation. The rate pressure product (RPP) was calculated as a surrogate of oxygen consumption from left ventricular pulse pressure (PP\(_{LV}\)) and heart rate (HR) as:

\[
RPP = PP_{LV} \cdot HR
\]  

(1)

There was no direct measurement of coronary sinus pressure and we used left ventricular diastolic pressure (LVDP) as a substitute, since it is closely related to right atrial pressure. LVDP was derived as the minimum value of PLV during mid-diastole, i.e. avoiding the small dip in early diastole. With this, per-beat coronary microvascular resistance (MR) was calculated as the difference between mean distal coronary pressure and LVDP divided by mean flow velocity.

**Wave Intensity Analysis**

Wave intensity \((dI)\) is defined as the product of incremental changes in local pressure \((dP)\) and flow velocity \((dU)\). Coincident forward \((dI^+\)) and backward \((dI^-)\) travelling waves are superimposed to form the net wave intensity at the measuring location [17].

Net wave intensity (in Wm\(^{-2}\)s\(^{-2}\)) was calculated from the ensemble-averaged cycles during the VM and normalized for the sampling rate by

\[
dI = \frac{dP}{dt} \cdot \frac{dU}{dt}
\]  

(2)

The separate forward and backward contributions were obtained as [1]

\[
dI_1 = \frac{1}{4pc} \left( \frac{dP}{dt} \pm pc \frac{dU}{dt} \right)^2
\]  

(3)

where \(\rho\) is the blood density (1060 kg·m\(^{-3}\)) and \(c\) is the wave speed (in m·s\(^{-1}\)) determined by the single-point technique [18]. The wave speed for wave separation was derived from the same signals used to derive the net wave intensity. The energy (in Jm\(^{-2}\)s\(^{-2}\)) carried by each wave was quantified by integrating the area under each of the separated dominant waves.

Waves are characterized by their direction, and their effect on pressure and flow. Pressure and flow change together in forward waves but in opposite ways in backward waves. Compression waves increase pressure while expansion waves decrease pressure. Thus, waves can be classified into four types: Forward compression wave (FCW), forward expansion wave (FEW), backward compression wave (BCW) and backward expansion wave (BEW). The FCW and BEW are flow accelerating waves while BCW and BEW are flow decelerating waves. Thus, in a coronary artery, a BEW caused by myocardial relaxation decreases pressure but accelerates the flow along the vessel [2].

**Statistical analysis**

All values are expressed as mean ± standard error of the mean unless specified otherwise. The means within the same step of the VM, e.g. different wave energies were compared using a paired Student’s t test. Results from different phases of the VM were compared to baseline and to the previous step using ANOVA with
repeated measures followed by contrast analysis (SPSS v. 19.0, IBM, Armonk, NY). Relationships between variables were investigated with linear regression analysis (Grapher v. 8.7, Golden Software Inc., Golden, CO). A value of $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics
The mean age of the subjects was 57 ± 9 years (Table 1). The study vessels were minimally diseased with a diameter reduction of 20 ± 9%. Most measurements were obtained in the left anterior descending and left circumflex coronary artery.

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics (n=13)</th>
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<tr>
<td>Age, yrs</td>
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<tr>
<td>Male gender</td>
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<tr>
<td>Diameter reduction (%)</td>
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<tr>
<td>Study vessel (LAD/LCX/RCA)</td>
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<tr>
<td>Coronary risk factors</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypertension</td>
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<td>ACE inhibitors</td>
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<td>Calcium antagonists</td>
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<td>Nitrates</td>
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Values are mean ± SD or n (%). LAD, left anterior descending artery; LCX, Left circumflex artery; RCA, right coronary artery.

Hemodynamic variables during the VM
None of the patients experienced anginal episodes during the VM and all were able to perform at least one successful VM. Figure 1 shows a representative example of the signals recorded during the VM. The effect of the VM on the systemic and coronary circulation is demonstrated by the typical course of the pressure waveforms. At the onset of strain (S1), all pressures briefly increased due to the sudden rise of pressure in the thoracic cavity. With continued strain (S2), reduced venous return impedes filling of the left ventricle and produces a decreased blood pressure and baroreflex-mediated increased heart rate, as well as a decline in the systolic-diastolic difference in PLV. The elevated LVDP during the strain reflects the increase in thoracic pressure induced by the VM. Upon exhalation, intrathoracic pressure returns to normal values and this release of strain (R1) rapidly restores LVDP and induces a short-lived drop in blood pressure followed by filling of the thoracic vasculature. The recovery is characterized by an overshoot in blood pressure due to increased venous return and a declining heart rate (R2), with all signals returning to baseline values (B2).
Figure 1: Simultaneous systemic and intracoronary hemodynamic recording during the Valsalva manoeuvre. Top panel (from top to bottom): Alteration in aortic (P_a), coronary (P_d), and left ventricular pressure (P_{LV}) as induced by the VM. Phasic and mean coronary flow velocity (U); mean coronary microvascular resistance (MR), and heart rate (HR). Shaded areas indicate cardiac cycles analysed at baseline (B1, B2) and during periods corresponding to the typical phases of strain (S1, S2) and release (R1, R2) of the VM. There is an immediate and sustained increase in left ventricular diastolic pressure during the strain period. The lower panels show the transition at the onset of strain, S1, and at the sudden release, R1, at an expanded time scale.
Despite these distinct changes in pressure, coronary blood flow remained remarkably constant. Flow velocity (U) was briefly diminished in the early compression phase S1, but returned to baseline values with continued strain. After restoration of respiratory outflow in R1, a reactive hyperemic response is noticeable, despite an increase in mean coronary microvascular resistance (MR). MR declined gradually during the strain phase and slowly increased during the release except for the transients at the onset and release of VM in this example as illustrated in the lower panels of Fig. 1.

The overall responses of hemodynamic variables induced by the VM are summarized in Fig. 2. Panel A depicts the mean pressures measured at the different phases. LVDP, which on mechanistic grounds most directly reflects the effect of changes in intra-thoracic pressure, more than tripled at the onset of strain, from 11 ± 2 mmHg at B1 to 36 ± 3 mmHg at S1 (p<0.001), then decreased slightly at S2 (p<0.005) and essentially returned to baseline level upon release of the strain, R1. The responses of mean aortic and coronary pressure practically coincide and follow the pattern described in relation to Fig. 1. Compared to baseline, these arterial pressures were 26% higher at S1, followed by a 14% and 24% depression during S2 and R1, respectively, and a 16% overshoot at R2 (all p<0.005). Changes in aortic pulse pressure paralleled those in left ventricular pulse pressure (Fig. 2B). Despite the marked increase in mean pressures, the pulse pressures were not affected by the initial strain at S1, with aortic pulse pressure (PPₐ) remaining at about 57 mmHg and left ventricular pulse pressure (PPₗᵥ) at 125 mmHg. With continued strain (S2), both pulse pressures dropped to much lower values, PPₐ to 21 ± 2 mmHg and PPLV to 77 ± 6 mmHg. Similarly, the pulse pressures remained low (<10% change) at the early release R1, but then regained the initial amplitude quickly with a 13% overshoot at R2 compared to the initial baseline (p<0.005).

Heart rate (Fig. 2C) remained rather stable throughout the VM, and the largest change was a 13% increase at R1 compared to baseline (p<0.005).
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LVdP/dt during both contraction and relaxation (Fig. 3A) followed a pattern similar to the pulse pressures, with a 25% and 39% reduction (p<0.005) for the upslope and downslope, respectively, during the maximum strain S2 and early release R1. The rise and fall of LV pressure were not affected by the initial strain at S1 and had a small (<14%) overshoot at R2. Commensurate with the changes in LVdP/dt, the parameter reflecting oxygen consumption, RPP (Fig. 3B), was not affected by the initial strain S1 and increased by 22% during the recovery at R2 compared to baseline (p<0.05). Like LVdP/dt, RPP was markedly reduced by 38% at maximum strain (S2) and by 21% during the early release (p<0.005).
In contrast, mean coronary blood flow velocity (Fig. 3C) was only minimally reduced by 12-16% (p<0.05) during the VM strain. This likely reflects changes in the coronary microcirculation due to both autoregulatory mechanisms and mechanical influences related to extravascular compression. The reactive hyperaemic response at R2 depicted in Fig. 1 was absent in 23% of the patients and on average, the peak reactive flow velocity was not different from control. As can be seen in Fig. 3D, calculated values of average MR were substantially decreased by 31% at S2 and elevated by 25% at R2 (both p<0.005), with no change immediately after altering intrathoracic pressure at S1 and R1. Note that all hemodynamic values returned to baseline at the end of the manoeuvre.

**Coronary wave intensity pattern during the VM**

The mean wave speed during the VM is depicted in Fig. 4. The baseline value before the VM (B1) was 18.7 ± 2.2 m·s⁻¹. At maximum strain (S2) and early release (R1) the wave speed decreased by almost 50% (p<0.001) to respectively, 10.3 ± 1.2 m·s⁻¹ and 9.4 ± 1.2 m·s⁻¹. There was no statistical difference between wave speed measured in the LAD (n=5) and LCX (n=7). Since there was only one RCA no statistical inference can be drawn for this vessel.

Typical examples of hemodynamic signals and associated coronary wave intensity obtained at the different phases of the VM are depicted in Fig. 5 for the same patient as in Fig. 1. In each panel, the ensembled pressure and flow velocity waveforms are displayed above the corresponding net wave intensity profile (thick line) and its respective forward (positive) and backward (negative) components. In all subjects, coronary wave intensity demonstrated the four dominant waves produced by changes in the pressure and velocity signals during the cardiac cycle. A BCW occurred at the start of cardiac contraction when the aortic valve is still closed, followed by a FCW as soon as the valve opened. With the onset of cardiac relaxation a FEW appeared as pressure decreased, followed by a BEW. Concomitant with the depression in coronary pressure amplitude at maximum strain (S2) and early release (R1), the intensity of all waves was reduced in size, while they increased in magnitude during the pressure overshoot in R2. Incidentally, an extra wave was observed in mid-systole during the maximum strain (S2) and sudden release (R1) of the VM (arrows in Fig. 5). These extra waves appeared in 8 patients during the VM and comprised both flow accelerating and decelerating waves.

Fig. 6 shows the overall variation in the energy of the separated coronary waves during VM. Both forward waves arriving via the aorta during contraction (FCW) and relaxation (FEW) were similarly affected by the strain of the VM (Fig. 6A). They did not change at the initial strain S1, but decreased by about 46% from baseline to maximum strain at S2 (p<0.005). The low values reached at S2 were maintained within 8% at the early release R1 although the difference was significant (p<0.005). Both forward waves returned to baseline values, with first a 51% overshoot at R2 in the FEW (p<0.005). The FCW remained significantly higher than the FEW throughout the VM (p<0.005).
Figure 3: Cardiac and coronary hemodynamic variables during the Valsalva manoeuvre. A. Left ventricular speed of contraction (upslope) and relaxation (downslope) in terms of LVdP/dt. B. Rate pressure product (RPP). C. Coronary flow velocity (U). D. Coronary microvascular resistance (MR). The strain clearly lowers cardiac performance, oxygen consumption, and coronary resistance, while mean flow velocity stays essentially constant. *p<0.05, **p<0.005 compared to baseline B1; §p<0.05, †p<0.001 compared to the previous step.

Figure 4: Coronary wave speed during the Valsalva manoeuvre. The wave speed is reduced during the strain. *p<0.05, **p<0.005 compared to baseline B1; ‡p<0.05, §p<0.001 compared to the previous step.
**Figure 5:** Changes in coronary wave intensity pattern during the Valsalva manoeuvre.

Example of ensembled coronary hemodynamic waveforms and corresponding wave intensity ($dI$) pattern at the different phases of the VM (same patient as shown in Fig. 1). B1, B2: baseline before and after the manoeuvre. S1, onset of strain; S2 sustained strain; R1, early release; R2, late release. Net wave intensity ($dI$) is indicated by a thick line and separated forward and backward components ($dI_{±}$) by thin lines; light grey fill: flow accelerating waves (FCW and BEW); darker grey fill: flow decelerating waves. The typical wave intensity pattern is depressed at maximum strain (S2) and early release of the VM (R1), and has a higher magnitude at late release (R2). Extra waves appeared in mid-systole, at S2 and R1 (arrows).
Figure 6: Energy of separated coronary waves during the Valsalva manoeuvre and their relationship with LVdP/dt.
A. Forward compression (FCW) and expansion waves (FEW); B. backward compression (BCW) and expansion waves (BEW). The energy of all dominant waves is reduced during the strain. C. Energy of forward waves and D. Energy of backward waves vs. LVdP/dt as a measure of the speed of cardiac contraction (compression waves) and relaxation (expansion waves). Note that flow accelerating waves (FCW and BEW) have a higher energy at the same LVdP/dt. *p<0.05, *p< 0.005 compared to baseline B1; †p<0.05, †p< 0.001 compared to the previous step.
In contrast, the strain of the VM had a larger effect during the relaxation than during the contraction on the waves originating from the microcirculation (Fig. 6B). At maximum strain S2, the energy of the BCW dropped by 33% (from $5.2 \pm 0.7$ to $3.5 \pm 0.4 \times 10^3 \text{ Jm}^{-2}\text{s}^{-2}$) ($p<0.05$) while the energy of the BEW decreased by 63% (from $6.1 \pm 0.9$ to $2.3 \pm 0.6 \times 10^3 \text{ Jm}^{-2}\text{s}^{-2}$) ($p<0.001$). This caused the BEW to become significantly lower than the BCW ($p<0.001$) at maximum strain S2 and sudden release R1, while the opposite is true ($p<0.01$) at baseline or during the other phases of the VM (S1 and R2). The initial strain S1 did not alter the energy of these backward waves, and the low values at S2 did not increase by more than 15% at the early release R1, although this was statistically significant for the BEW ($p<0.005$). Notably, in the recovery phase R2, the BEW more than tripled from R1 (to $8.0 \pm 0.6 \times 10^3 \text{ Jm}^{-2}\text{s}^{-2}$), while the BCW rose by 70% to $6.8 \pm 0.3 \times 10^3 \text{ Jm}^{-2}\text{s}^{-2}$ ($p<0.05$).

In general, the energy of the separated coronary waves followed the pattern of cardiac mechanics parameters such as aortic pulse pressure (Fig. 2B), LvdP/dt and RPP (Fig. 3A and 3B) during the phases of the VM, rather than that of coronary MR or flow velocity. As shown in Fig. 6C, the mean energies of the separated waves were remarkably well related to the respective LvdP/dt regardless of the nature of the wave. Notably, at similar LvdP/dt, flow accelerating waves that favour forward flow (FCW and BEW) had more energy than flow decelerating waves impeding inflow (BCW and FEW) suggesting an easier filling of the intramural resistance vessels.

**DISCUSSION**

The major findings of this study can be summarized as follows: 1) Coronary wave intensity is not affected by sudden changes in average values of aortic and left ventricular pressure induced by the VM strain, but rather by sustained changes in parameters related to cardiac function such as LvdP/dt. 2) Counter-intuitively, the strain period is associated with a decrease in coronary MR despite the substantial reduction in oxygen consumption-related parameters and as a result, beat-averaged coronary flow velocity remains rather constant during the VM. 3) The reduced strength of contraction is a major determinant of the decrease in MR and reflects the reduced extravascular component of coronary resistance. 4) Coronary wave intensity primarily reflects the dynamics of contraction-coronary perfusion interaction rather than being directly related to mean coronary flow.

**Physiological responses invoked by the Valsalva manoeuvre**

Cardiovascular responses to the Valsalva manoeuvre induce striking changes in arterial pressure, which are related to shifts in blood volume from the thoracic to splanchnic region, impeded venous return and reduced stroke volume, and an increase in peripheral resistance [19-20]. These systemic mechanical responses are nicely demonstrated in our measurements of aortic and LV pressure. In the absence of direct measurements of intrathoracic, left atrial or right atrial pressure, we assume that these pressures can be adequately approximated by LVdP [20]. Based on accepted mechanical principles, LV pressure is generated with respect to
pressure in its surroundings and according to intrinsic contractile properties of the heart and the filling of the ventricle. Because of the rapid changes in LVDP in the single beats in which the VM starts and stops (as illustrated in the lower panels of Fig. 1), it is reasonable to assume that diastolic filling and intrinsic contractile properties are not altered in this brief transient period. This assumption is consistent with the observation that parameters related to the force of contraction such as LV pulse pressure and LVdP/dt are not affected from B1 to S1 and only marginally from S2 to R1.

With continued strain, the limited venous return causes a decrease in LV pulse pressure, which also reduces the afterload and results in a decrease in LVdP/dt. The restoration of venous return from R1 to R2 and B2 re-establishes normal cardiac function as expressed by all pressure signals, with some overshoot in R2 caused by reflex-mediated nervous responses [14].

**Coronary blood flow and resistance during the Valsalva manoeuvre**

Conflicting observations have been reported previously on the effect of VM on coronary blood flow. Some studies [21] reported a decrease in coronary flow at maximum strain while others have observed no change [22-23] or even advocated a beneficial effect on coronary perfusion during ischemic episodes [24]. Mechanistically, coronary blood flow is determined by the coronary arterial-venous pressure difference and microvascular resistance, MR. As argued above and supported by earlier observations, LVDP may be assumed to reflect the outflow pressure of the coronary circulation [25]. MR can model-wise be considered as a series of two resistances [26-27], one influenced by control of vascular smooth muscle tone in the resistance vessels (Rc) and the other resulting from the vascular tree at full vasodilation (Rd). Rc is under the influence of metabolic control and consequently will increase with a decrease in oxygen consumption. Rd is determined by the intrinsic geometric properties of the vascular bed and blood viscosity, but also by compression of the intramural vessels during cardiac contraction. This compression effect is often referred to as extravascular resistance and increases with heart rate, LV pressure generation, and LVdP/dt [28-29].

In the present study, we found almost no effect of sustained strain on coronary flow velocity in our patient group. This finding is surprising in light of the reduced oxygen consumption following the 38% reduction of the RPP at maximum strain (S2), which should normally have resulted in a matched decrease of coronary blood flow. In terms of metabolic control, one would have expected a vasoconstrictor effect on Rc and hence, an increase in total MR. It should be noted that a decrease in arterial-venous pressure gradient attenuates the vasodilatory effect of oxygen consumption on Rc, but this can never result in a flow that remains independent from oxygen consumption. The reduced MR at S2 must be found in Rd, which is contraction-dependent. Hence, the decrease in generated LV pressure and LVdP/dt results in a diminished extravascular compression and reduced Rd that fully compensates the vasoconstrictor effect of the lower oxygen consumption during the VM strain. Similar reasoning explains why coronary flow velocity stays rather constant despite the increase in RPP at the release of intrathoracic pressure. The higher oxygen consumption induces vasodilation manifested by a decrease in Rc, which however is compensated by an increase in Rd following the restored LV
pressure generation and LVdP/dt. One should note that the transient response of Rc is slower than that of Rd [30-31], but incorporating these transients would require more detailed analysis that is beyond the scope of this study.

Coronary wave intensity during the Valsalva manoeuvre
In the past, the interaction of cardiac contraction and coronary perfusion has been studied with focus on systolic and diastolic differences in coronary flow. In animal studies, where coronary pressure can be kept constant with a perfusion system, this has been a rather helpful approach [32-34]. In humans, these variations are more difficult to dissect because of various interfering effects. A real advantage of wave intensity analysis is that time-dependent variations in pressure and flow signals during the cardiac cycle are jointly incorporated and wave intensity thus combines in one variable the effect of cardiac mechanics on coronary hemodynamics.

Our findings clearly demonstrate that coronary wave intensity is not influenced by absolute values of LV and aortic pressure, unless a change in pulsatile components occurs. It is also clear that one has to be very careful in directly relating wave intensity or energy to myocardial perfusion since there was a strong effect of the VM strain on wave energy at S2 and R1, but only a very minor change in coronary flow velocity. Hence, although similar mechanisms are involved in coronary wave generation and net perfusion of the heart, there is no direct and simple relation between the two.

The four separated waves appear strongly dependent on the contraction and relaxation function of the heart as assessed by LVdP/dt. This agrees with earlier findings on coronary compression waves in animals, where contractility was changed with paired pacing [35]. However, LVdP/dt should not without reservations be equated to contractility because it is afterload dependent [36], which is strongly altered during a VM. In the present study the waves promoting inflow into the microcirculation, FCW and BEW, contain more energy than the waves opposing inflow, BCW and FEW for the same LVdP/dt. This suggests that the microcirculation is easier filled than emptied especially when LV pulse pressure is high such as in R2.

As was pointed out in relation to Fig. 1, extra waves where sometimes detected in mid-systole and are most likely related to reflected waves from the aorta [20]. These reflected waves can reach the coronary vessels either as forward waves via the coronary ostium or as backward waves by transmission via the LV cavity depending on the arrival time during the cardiac cycle and on the myocardial stiffness.

Study Limitations
We could not ensure that the VMs were performed in the same way by our patients, which may have affected the individual hemodynamic responses. However, in all patients, the typical changes could always be observed and the data were summarized for the representative cycles of each phase.

Wave intensity analysis is performed from the derivatives of pulsatile signals, of which especially the recorded Doppler velocity signal can be noisy. Although all signals were filtered first, ensemble averaging helps to further reduce the noise and even three beats produced much smoother results than one. However, during
the VM the signals go through big changes within a few beats. Thus we tried to find the best compromise between averaging over a sufficient number of beats to reduce the noise and taking the minimum number of beats to avoid loss of information especially during the onset (S1) or release (R1) of strain. Our protocol did not allow for performing a VM during maximal vasodilatation induced by continuous intravenous administration of adenosine. Such an experiment would be a useful since it allows studying the extravascular component of coronary resistance after elimination of vasoactive control.

Local wave speed in the coronary is essential for wave separation. The single-point method [18] is, however, not optimal in coronary arteries because it has been shown that vasodilatation of the resistance vessels or the presence of a stenosis proximal to the site of measurement affects the calculated local wave speed [37-38]. However, our present measurements were performed in a reference vessel without pharmacological vasodilation and the values of coronary wave speed we obtained compare well to those reported in healthy coronary arteries of dogs [39] and humans [4]. The observed decrease in wave speed during the VM strain is to be expected, since transmural pressure is substantially lower during this period and hence, the vessel wall becomes more compliant.

The relationship between wave speed and wave intensity is not straightforward as is clear from Eq. 3 and lowering calculated wave speed was shown to increase separated wave intensity [37]. In contrast, we observed a decrease in wave intensity during the VM strain period when wave speed was low. We may therefore conclude that our results on changes in separated energies are not confounded by the measured changes in wave speed. Moreover, net wave intensity does not depend on wave speed and we showed earlier that the net waves demonstrated similar changes during the VM as the separated waves reported here [40].

**Clinical implications**

Our results demonstrate that coronary waves as defined by wave intensity are strongly dependent on the contractile function of the heart and that the reduced compression on the coronary microcirculation by cardiac contraction not only results in waves with less energy, but also in a decreased extravascular resistance promoting perfusion of the myocardium. In terms of supply and demand ratio, a VM may be beneficial for myocardial perfusion not only because the drop in RPP indicates a lower oxygen consumption during the strain, but also because of the reduction in extravascular resistance. This forms a theoretical basis for the pain relief induced by a VM in patients with acute ischemia as reported earlier [24] as well as the absence of any ischemic complaints from our patients who performed the VM prior to revascularization of the culprit stenosis in a different vessel.

The VM may thus be developed into a clinical test for the functional interaction between cardiac contraction and coronary hemodynamics and thereby support the validation of multi-scale models of the coronary circulation currently under development.
CONCLUSION

Coronary wave energy is directly influenced by cardiac mechanical factors such as LVDp/dt and LV pulse pressure and rather poorly related to coronary flow, contrary to previous claims. Coronary resistance is not only subject to metabolic control but also to contraction-related extravascular resistance, which in case of the Valsalva manoeuvre can be of comparable weight. The VM may thus be a useful intervention for validating the predictive power of *in silico* models of the coronary circulation.
REFERENCES