Womersley number-based estimation of flow rate with Doppler ultrasound: Sensitivity analysis and first clinical application

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Abstract

In this paper we continue in investigating the approach we have proposed in a paper recently published, for a reliable estimate of (peak systolic) blood flow rate from velocity Doppler measurements. Basic features of this approach together with some in silico test cases were discussed in that work. Here, we provide more insights of this approach by performing a sensitivity analysis of the formulas relating blood flow rate to velocity. In particular we analyze how our estimates are affected by perturbation or errors in measurements in comparison with a standard method for catheter based estimates based on the assumption of a parabolic velocity profile. A first glance to in vivo clinical applications is given as well.

1. Introduction

The correct estimation of blood flow rate through a vascular surface is a major issue in clinical practice, since it could give important informations about the cardiovascular state of a patient. This can be pursued with a good precision by using different approaches, such as the Electromagnetic flow meter (see, e.g., [27,5]), the transit time thermodilution (see, e.g., [3]), the phase-contrast Magnetic Resonance Imaging (PC-MRI) (see, e.g., [1,2]) and the Doppler-based technique (see [10,15,35]). The latter approach estimates quite accurately blood velocity by measuring the difference in frequency between a transmitted wave and the reflected signal (Doppler shift effect). In particular in the continuous Doppler velocity the signal transmission is based on a continuous wave (see [12]), while in the pulsed Doppler...
velocity short pulses are transmitted (see [18]). Moreover, in the single-point Doppler method the reflected signal is retrieved in a single point of the vascular section. Other multi-gate devices acquire information over a large portion of the section. Among single-point Doppler techniques, one is based on the acquisition of the maximum velocity over the section at hand through the introduction of an intravascular guide-wire. The underlying assumption is that the sample volume is small compared to the vessel. Since only the maximum velocity can be measured, an assumption on the velocity spatial profile is needed in order to recover a flow rate estimate (see [20]). Within the multigate techniques no assumption concerning the velocity profile is needed since the velocity can be partially or totally retrieved. For example, with the uniform insonation method described in [12] an estimate of the mean velocity is obtained by the spectrum measured by the Doppler. However, sufficient uniformity of the sample volume is difficult to achieve (see, e.g., [17]). Alternatively, other techniques allow to estimate the whole velocity profile at the section at hand, under the assumption that the sample volume is large compared to the vessel, without any further hypothesis on the velocity across the section (see, e.g., [52,28]). Finally, Color Doppler technique allows to measure the Doppler shifts in a few thousand sample volumes located in an image plane (see, e.g., [53,30]). Unfortunately, this technique has a low velocity resolution and therefore it is mainly used for qualitative investigations (see [53]). In [54] a combination of pulsed-wave Doppler and Color Doppler has been proposed to overcome the limitations of both these techniques. Nowadays none of such techniques seems to be closer to a standard clinical practice for the estimation of flow rate. Different techniques are well suited for different purposes. For example, the single-point Doppler is largely the most used to estimate the flow rate for small vessels such as coronaries, where other Doppler-based methods are hardly applicable. This is based in general on the assumption of a parabolic velocity profile for estimating flow rate from maximum velocity. This method works fairly well for small districts and is much simpler than other algorithms based on Doppler velocity (see [20,35]). Available highly accurate velocity measures at different anatomical sites make the single-point Doppler approach attractive also for other vascular districts (see [36,25]) in the pulmonary artery, [49,44] in the renal artery, [46] for the aorta and [57] for the great cardiac vein). Also for the determination of the stroke volume in the left ventricular outflow tract the conventional single-point Doppler method has been clinically widely accepted (see [8]). In this case, the estimation of the flow rate is based on the assumption of flat velocity profile.

There are mainly two estimates of the flow rate obtained with the single-point Doppler method used in the clinical practice. The flow rate at the peak velocity instant, that is the instant where the velocity at the center-line is maximum over the whole cardiac cycle (referred in the sequel as peak flow rate, see, e.g., [46,11,51]) and the time averaged flow rate, that is the mean value of the flow rate over the cardiac beat (referred in the sequel as mean flow rate, see, e.g., [44,49]). In this paper we mainly focus on the peak flow rate even if the mathematical approach is readily extended to other flow rate estimates, as we will point out (Remark 2.1).

It is worth stressing that the a priori assumption of spatial velocity profile (usually a parabolic one) required by the single-point Doppler method introduces a bias in any flow rate estimate with potentially remarkable consequences. For what concerns the mean flow rate, even if some authors supported using a parabolic velocity profile (see [6,29]), in more recent years this has been considered too simplistic and misleading (see [43,21,22]). The limitations obtained by estimating the peak flow rate by using a parabolic velocity profile have been pointed out in [40] where a mathematically more sophisticated approach has been proposed. In particular, a new parametrized formula linking the maximum velocity and the flow rate at the peak instant has been introduced, with an explicit dependence on the heart pulsatility that is discarded in the parabolic assumption. The quantitative estimation of parameters is based on new methods of Computational Fluid Dynamics (CFD) (see Section 2). In this paper we continue the investigation of this approach with a sensitivity analysis of the proposed formula with respect to the measures of the velocity and the diameter. We show that this formula has stability features comparable with the parabolic one (Section 3). Moreover the two methods, namely the one based on the parabolic assumption and the new one, are applied to a clinical dataset retrieved from the database of the CNR Clinical Physiology Institute of Pisa. In particular, we aim at estimating the coronary flow reserve (CFR) in a group of patients. Single-Doppler peak flow rate based on the parabolic assumption has become the standard practice for this application where the knowledge of CFR is needed, such as during catheterisation and in percutaneous transluminal coronary angioplasty (see, e.g., [24,23,19,31,58,32,4]). Comparisons between classical and new estimates suggest that the new approach introduces a significant improvement with no extra cost in medical devices or clinical procedures (Section 4).

2. The parabolic and the Womersley-based formulas

Let \( I \) be a cross-section of the vascular district at hand. The mass flow rate \( Q(t) \) through \( I \) is defined as

\[
Q(t) = \int_I \rho u \cdot n d\gamma,
\]

where \( \rho \) is the blood density (hereafter assumed to be constant), \( u(t, x) \) the blood velocity, \( n \) the normal unit vector and \( d\gamma \) the infinitesimal area element. As anticipated in the Introduction, we focus on the peak instant \( t \). In principle, the whole velocity field \( u(t, x) \) on \( I \) is needed for estimating \( \hat{Q} := Q(t) \). However, Eq. (1) can be rewritten in terms of the mean velocity value \( \hat{U} := U(t) \) as

\[
\hat{Q} = \rho \hat{U} \hat{A}
\]

where \( \hat{A} := A(t) \) and \( A \) denotes the area of section \( I \). Unfortunately, mean velocity \( \hat{U} \) is not available from measures. On the other hand, as pointed out in the Introduction, single-point Doppler velocimetry analysis provides reliable measures
of the maximum velocity at the peak instant $V_M := V_M(t)$ on $\Gamma$. Eq. (2) requires therefore an appropriate formula relating mean velocity $\hat{U}$ to the maximum one $V_M$. In current clinical practice it is usually assumed

$$\hat{U} = \frac{V_M}{2}. \quad (3)$$

This equation stems from the hypothesis of a parabolic spatial profile for the velocity. For this reason in the sequel Eq. (3) will be referred to as parabolic formula. Strictly speaking this formula assumes that blood flow is steady or quasi-static, laminar and Newtonian in a rectilinear cylindrical vessel (see [35]). These assumptions are far to be fulfilled in real situations (see, e.g., [47,39,50,7]). In particular, it has been pointed out by different authors the relevance of blood flow pulsatility on the velocity profiles ([59,14,35]). In [40] it has been proposed to quantify pulsatility with the adimensional index (called Womersley number)

$$W = \frac{\hat{D}}{2} \sqrt{\frac{2\pi f}{v}}. \quad (4)$$

Here $\hat{D} := D(t)$, $D$ is the vessel diameter, $v$ the blood viscosity and $f$ the main frequency of the heart beat. This choice was motivated by observing that $W$ can be evaluated by using the quantities retrieved during standard Doppler acquisition procedure. Obviously, a more accurate spectral evaluation of $V_M(t)$ would lead to better evaluation of the incidence of pulsatility and eventually to the flow rate, by taking into account more frequencies of the heart beat together with the main one. However, this would need specific acquisition procedures and it would be not of practical use.

The higher the value of $W$ the more the assumption of parabolic velocity profile is incorrect (see, e.g., [59,14,35,40]). In [40] improved blood flow rate estimates from maximum velocity $\hat{V}_M$ could be fitted following the same guidelines. Which is the best approach for flow rate estimations (from [6a]) we recover the parabolic formula (3). However, for the same reason formulas (6) are more delicate in terms of sensitivity from the data, being estimates possibly polluted by error on maximum velocity $\hat{V}_M$, diameter, frequency and viscosity measures. On the contrary, parabolic formula (3) is independent of frequency and viscosity. This means that error in measuring these parameters do not affect the estimate. On the other hand, this formula is unable to account for flow rate modifications induced by a physical change of viscosity or pulsatility, as we have pointed out. In the next section we investigate with more detail the sensitivity of the different formulas on the parameters that are subject to measures, so to quantify the impact of possible errors on the final estimates.

**Remark 2.1.** It is worth pointing out that from the mathematical viewpoint the time when the velocity is measured is not relevant. In other words, our procedure can be carried out for any given instant $t$ when $V_M(t)$ is collected. A formula similar to (6) can be fitted in the same manner. This means that our approach is readily extended for evaluating also the minimal flow rate, if $V_M$ measures are available when the maximum (in space) velocity is minimal over the heart beat. If a sequence of measurements $V_M(t_i)$ for $i = 1, 2, \ldots, N$ is available, a time average of the maximum velocity and of the corresponding flow rates can be computed so to have an estimate of the mean flow rate. Alternatively, an ad hoc formula still in the form (6) for the mean flow rate could be fitted following the same guidelines adopted for the peak flow rate. Which is the best approach for evaluating the mean flow rate is still an open question and it could be subject of future developments of the present work.
3. Sensitivity analysis

3.1. Amplification factors

In order to evaluate sensitivity on measurements errors of formulas (6) in comparison with (3), we introduce an index \( \lambda \), called amplification factor, as follows. Let us consider a generic function \( y = y(x) \). Suppose that \( x \) could be subject to perturbations \( \delta \) possibly induced by measurements errors. Our goal is to evaluate the ratio between the relative errors, namely

\[
\lambda = \frac{(y(x + \delta) - y(x))/y(x)}{\delta/x} = \frac{y(x + \delta) - y(x)}{y(x)} \cdot \frac{x}{\delta}.
\]

Let \( \delta \) tends to 0, so we finally obtain

\[
\lambda = \frac{dy}{dx} \cdot \frac{x}{y}.
\]

This amplification factor states the impact of a perturbation on \( x \) on the result \( y(x) \). In the context of numerical analysis, \( \lambda \) is called condition number of \( y(x) \) (see, e.g., [45]). Observe that from the definition we have

\[
y(x + \delta) \approx y(x) \left( 1 + \lambda \frac{\delta}{x} \right).
\]

The approximation being good for \( \delta \) small enough. When quantity \( y \) depends on more variables \( x_j, j = 1, 2, \ldots \), partial derivatives are to be taken into account in order to weight the dependence of \( y \) on each independent variable \( x_j \) separately. In this way, the sensitivity indexes read \( \lambda_j = (\partial y/\partial x_j)(x_j/y) \). Large values of \( \lambda \) mean that small perturbations on \( x \) (due, for example, to an error in the measurement) could strongly affect the estimate \( y \). The sensitivity of the estimate has not to be confused with its accuracy, that is how this estimate \( y \) is “close” to the real value \( y_{\text{ex}} \). Hereafter, we focus our attention on the dependence of our formulas on the measure of the maximum velocity and of the diameter, which are those parameters in formulas (3) and (6) likely to be most operator-dependent.

3.1.1. Sensitivity to the maximum velocity

All the proposed formulas depend linearly on \( \hat{V}_M \), i.e., are in the form

\[
\hat{Q} = c(W) \hat{V}_M,
\]

where \( c(W) \) is a function of the Womersley number (and in particular a constant for the parabolic formula (3)). From (8) we have for all the formulas considered here

\[
\lambda_{\hat{V}_M} = \frac{\partial \hat{Q}}{\partial \hat{V}_M} \frac{\hat{V}_M}{\hat{Q}} = c(W) \hat{V}_M \frac{c(W)}{c(W)\hat{V}_M} = 1.
\]

Sensitivity of the formulas to maximum velocity measures is therefore the same. A possible error \( \delta \) on this measure affects flow rate estimates, both with the parabolic and with the Womersley-based formula with a perturbation of the same order of \( \delta \).

3.1.2. Sensitivity to the diameter

Sensitivity on the diameter \( \hat{D} \) is even more critical with respect to the operator skills and experience. The sensitivity index related to \( \hat{D} \) is given by

\[
\lambda_{\hat{D}} = \frac{a \hat{Q} \hat{D}}{a \hat{D} \hat{Q}},
\]

where \( \hat{Q} \) is one of the formula for the estimation of the flow rate. By a simple application of (11) and recalling that \( \hat{A} = \pi \hat{D}^2/4 \), we obtain the following sensitivity indexes:

1. Parabolic formula: in this case we have from (3)

\[
\lambda_{\hat{D},\text{parabolic}} = \frac{a \pi \hat{D} \hat{V}_M}{4} \left( \frac{\hat{D}}{(\nu/2)(\pi \hat{D}^2/4)\hat{V}_M} \right) = 2.
\]

2. Womersley-based formula for small Womersley numbers: from (6a), by algebraic manipulation we have

\[
\lambda_{\hat{D},g_1} = 2 + b_1 \frac{a_1 \hat{W}^{b_1}}{1 + a_1 \hat{W}^{b_1}}.
\]

3. Womersley-based formula for large Womersley numbers: from (6b), we obtain

\[
\lambda_{\hat{D},g_2} = 2 + \frac{a_1 \hat{W}}{(1 + a_1^2 \hat{W}^2)^{1/2}} \arctan(a_1 \hat{W}).
\]

4. Womersley-based formula for intermediate Womersley numbers (Eq. (6c)): in this case computations are made more difficult by the presence of the weight function \( w \) that depends on \( \hat{D} \) through the Womersley number. Let us introduce the following notation:

\[
\gamma_{12} = \frac{w g_1}{(1 - w)g_2}, \quad \gamma_{21} = \frac{(1 - w)g_2}{w g_1}, \quad \gamma_w = \frac{w'}{w} \hat{D},
\]

\[
\gamma_{w12} = \frac{g_1 - g_2}{g_2} \hat{D}.
\]

Then, it is possible to verify that

\[
\lambda_{\hat{D},g_{12}} = 2 + \left( \frac{1}{\gamma_{21}} + \frac{1}{\gamma_{12}} \right) + \frac{1}{\gamma_w + \gamma_{w12}}.
\]

3.2. Forward and backward analysis of perturbations

Sensitivity analysis can be profitably used for evaluating the accuracy of the flow rate estimates in presence of measurement errors.

Computation of a dependent variable \( y = y(x) \) based on a measure of the independent one \( x \) is affected by two kind of errors. The first one is the measurement error on \( x \). The second one is the approximation introduced by the estimation itself. In the forward sensitivity analysis introduced in the previous section the effects of perturbations of \( x \) on the final results are considered. In the backward analysis, errors are evaluated by quantifying perturbations to be impressed on the original data set such that, with the approximated estimation procedure, the final estimation is exact.

With reference to Fig. 1, the solid line corresponds to the exact calculation of \( y_{\text{ex}} \) in \( \hat{x} \), whilst the dashed line corresponds to the approximated computation which leads to \( y_{\text{approx}}(\hat{x}) \).
Then, in the spirit of the backward analysis, we look for the perturbation on the data $\delta$ such that the approximated computation applied to the perturbed data $x + \delta$ is equal (or at least “close”) to the exact value, namely $y_{\text{app}}(x + \delta) = y_{\text{ex}}(x)$. In other words, we look for a perturbation $\delta$ that compensates the approximation of the process. Actually, we look for $\delta > 0$ such that

\[
|y_{\text{ex}} - y_{\text{app}}(x + \delta)| < |y_{\text{ex}} - y_{\text{app}}(x)|. \tag{16}
\]

Let us assume the following hypotheses:

**H1.** $x > 0$, $y_{\text{app}} > 0$, $y_{\text{app}} > 0$ (and then $\lambda > 0$).

**H2.** the approximation process is affected by a constant bias such that $y_{\text{app}}(x) < y_{\text{ex}}$.

By exploiting Eq. (9) and assuming that H1 and H2 hold, inequality (16) becomes

\[
y_{\text{app}}(x) - y_{\text{ex}} < y_{\text{ex}} - y_{\text{app}}(x + \delta) = y_{\text{ex}} - y_{\text{app}}(x) \left(1 + \lambda \frac{\delta}{x}\right)
\]

\[
\Rightarrow 2(y_{\text{app}}(x) - y_{\text{ex}}) < -\frac{\lambda y_{\text{app}}(x)}{x} < 0.
\]

Then, under the previous assumptions the latter inequality is solved by

\[
\delta < \frac{2(y_{\text{ex}} - y_{\text{app}})x}{\lambda y_{\text{app}}(x)}. \tag{17}
\]

Notice that as a consequence of our hypotheses, the right hand side is positive. This means that positive perturbation small enough on the independent data does not necessarily get worse estimates. If $\delta$ fulfills (17), measure based on $x + \delta$ is actually more accurate then on $x$. A small overestimation of $x$ can partially balance the intrinsic error in the approximated computation.

### 3.3. Results and discussion

#### 3.3.1. Sensitivity to the diameter

In Fig. 2 we illustrate the stability index $\lambda_D$ of the Womersley-based formulas as a function of $W$. We observe that for $W \leq 2.7$ and $W \geq 3.1$, Womersley-based formula is slightly more sensitive than the parabolic formula, as was to be expected since this formula actually depends on the Womersley number, that in turn depends on the diameter. In particular, for $W < 2.7$ the sensitivity increases with the Womersley number, while for $W > 3.1$ it decreases with $W$. In this range, the increment of $\lambda_D$ is in any case less than 13% of the index of parabolic formula.

On the contrary, for $2.7 < W < 3.1$, we observe that the amplification factor increases up to 68% with respect to the index of parabolic formula. This stems from the fact that in this range of the Womersley number, our formula is given by a weighted linear combination of $g_1$ and $g_2$. In the superimposition of the effects the amplification factor is affected by the sum of the two contributions. In order to reduce the sensitivity of the “weighted” Womersley-based formula, we modify the weight function $w(W)$ in (6). In particular, we propose the linear function

\[
w(W) = \frac{3.1 - W}{0.4}. \tag{18}
\]

From the mathematical viewpoint, this choice introduces a less regular function. Indeed, the Womersley-based formula over the entire range of physiological ranges of Womersley numbers will be only continuous, with discontinuous derivatives. However, it reduces the sensitivity to $\hat{D}$ of the Womersley-based formula in the range $W = (2.7, 3.1)$, as shown in Fig. 2, since it features a slope smaller than with the weight (7). The amplification factor reduces to 38% more than the one of parabolic formula.

It is important to outline that, while the stability of the Womersley-based formula with weight (18) is greatly improved, the accuracy is maintained. This is confirmed by numerical results referring to the same in silico validation test cases considered in [40]. We apply the original and the modified Womersley-based formula (given by weights (7) and (18), respectively) to the brachial flow wave test case. The results in Table 1, show that the accuracy of the Womersley-based formula is not worsened.
To be more concrete, we detail some examples of clinical relevance (in all the examples we set $\nu = 0.035$ Poise).

(1) Coronary vessel: Let us consider the measure of flow rate at the peak instant in a coronary vessel. We assume that the diameter of such a district at that instant is $\hat{D} = 2$ mm. In basal conditions, frequency $f = 1$ Hz, consequently $W = 1.34$. For example if the error in the measurement of the diameter were equal to 10%, the perturbation induced by the parabolic formula would amount to 20% (see (12)), while from (13) it follows that the perturbation of the Womersley-based formula would amount to 20.6%.

If an applied stimulation elicits an increase in cardiac chronotropism, such as during pharmacological stress test (dobutamine) or physical stress, like during exercise, the heart rate may increase two–three-fold with respect to baseline values. In these circumstances the Womersley number will increase. In particular, if we assume $f = 3$ Hz, corresponding to $W = 2.32$, the perturbation of the Womersley-based amounts to 22.8%.

(2) Brachial artery: Let us consider the brachial artery: in this case, a possible value of the diameter is $\hat{D} = 4.2$ mm and then the Womersley number in basal conditions ($f = 1$ Hz) would be $W = 2.81$. In this case we refer to the perturbation (15) of the weighted formula (6c) with weight (18). With a 10% error in the diameter measure, the perturbation of the Womersley-based formula given by (15) would be of 37.4% (20% for the parabolic formula).

(3) Femoral artery: Here we can assume $\hat{D} = 10$ mm. In basal conditions we have $W = 6.69$ and the perturbation of the Womersley-based formula given by (14) would amount to 21.0%, while under adenosine we have $W = 11.60$ and the perturbation would be of 20.5%, versus the 20% of the parabolic formula.

3.3.2. Overestimation of the measures

Referring to Section 3.2, in our application the datum $x$ is the diameter $\hat{D}$ or the maximum velocity $\hat{V}_M$ at the peak instant, whereas the calculations $\hat{V}_e$ and $\hat{V}_{app}$ are the exact and the estimated flow rates at that instant $\hat{Q}_e$ and $\hat{Q}_{app}$, respectively.

Let us focus on the parabolic formula, that is $\hat{Q}_{app}$ is given by (3). It is worth noting that clinical evidence (see, e.g., [7]) suggests that parabolic formula underestimates the real flow rate, $\hat{Q}_e > \hat{Q}_{app}$. In other words, there is a systematic error with a constant bias (i.e., $\hat{Q}_e - \hat{Q}_{app} > 0$). Moreover, we remark that $\hat{D} > 0$, $\hat{V}_{app} > 0$ (if we focus on downstream fluxes) and $\hat{Q}_{app} = \hat{Q}_{app} / \hat{D} > 0$ for construction. This means that $H_1$ and $H_2$ in Section 3.2 hold and we can apply (17).

For example, using one of the in silico test case shown in [40], we have $\hat{V}_M = 442.10$ mm/s, $\hat{D} = 1.2$ mm, $\hat{Q}_e = 1000$ mm$^3$/s, $\hat{Q}_{app} = 987.6$ mm$^3$/s, $W = 1.737$. From (10), (12) and (17), it follows that an error on the maximum velocity at the peak instant fulfilling $0 < \delta < 11.102$ mm/s leads to a better estimate of the flow rate. A small positive perturbation on the measures of $\hat{V}_M$ and $\hat{D}$ can improve the flow rate estimate based on (3).

4. Some steps to “in vivo” validation

Validation of (6) in [40] was based on CFD results, by performing numerical simulations in geometries and regimes different from the ones used for fitting the parameters in such formula. In [41] Womersley-based formulas have been applied to Y-graft bypass. The advantage of in silico test cases is that prescription and comparison of data is completely under control. Results obtained in this way show that Womersley-based formula can significantly improve flow rate estimates at the peak instant in comparison with parabolic formula.

Our next step is in vivo validation. In what follows we provide a first clinical application of the Womersley-based formula. We point out that this application is just preliminary, even if it is an important step in that direction.

Among all the clinical flow rate applications, we have focused on catheter-based Doppler ultrasound velocimetry analysis for the measurement of the CFR. We point out that if the shape of the velocity profiles at the two conditions were the same and the area could be assumed constant, the CFR could be estimated with a good precision by the ratio between the velocities. However, in [43] it has been pointed out that this assumption can be a source of error. For this reason, we need a good estimate of the flow rate to obtain a reliable CFR measure. In particular, a 2.9 F, 10 MHz intravascular ultrasound (IVUS) catheter (Eagle Eye Gold, Volcano Corp., San Diego, CA, USA) was passed over the flow wire. This application is one of the most relevant in clinical environment (see [13,32,4]). In particular, the CFR has been extensively used to assess coronary vasomotricity in patients with coronary artery disease (CAD) (see [48]). CFR is known to be defined as the ability of coronary vessels to increase blood flow adjusting it for the myocardium demands for oxygen and energy. CFR can be defined as the ratio between the flow rate $\hat{Q}_e$ measured at the peak instant in a coronary vessel during maximal vasodilation and the flow rate $\hat{Q}_e$ measured at the peak instant in resting conditions.

| Table 1 – In silico validation: comparison between the relative errors obtained with formulas (3) ($E^W$), (6b) with weight (7) ($E^E$) and (6b) with weight (18) ($E^W_{mod}$). |
|-----------------|-----------------|-----------------|-----------------|
| $W = 2.868$    | 18.42%          | 9.52%           | 8.03%           |
| $W = 3.049$    | 18.17%          | 2.77%           | 3.33%           |

In the case of Womersley-based formulas, there is no available experimental evidence of a constant bias in flow rate evaluation, so it is not possible at the moment to give any practical suggestions. Numerical in silico results presented in [40,41] suggest however that also this formula features a constant underestimation (even if sensibly reduced with respect to the parabolic one as will be illustrated in Section 4). If these results will be confirmed by in vivo validation, then the indication moving towards an overestimated value of the maximum velocity (and possibly of the diameter) will apply to the Womersley-based formula as well.
that is

\[
\text{CFR} = \frac{\hat{Q}_S}{\hat{Q}_R} \quad \text{(19)}
\]

Therefore, CFR could represent a clinical diagnostic and prognostic index concerning the coronary vessel ability to increase flow proportional to increases in myocardial metabolic demand.

We have applied the Womersley-based formula (6) to 13 subjects, 8 with idiopathic dilated cardiomyopathy and 5 without cardiac diseases (control group). To guarantee an unbiased process, this has been done in a blind fashion that means that we did not know *a priori* which of the patients were affected by an idiopathic dilated cardiomyopathy. The patients have been selected from the database of CNR of Pisa, Italy (see [33] for details). The patients signed an informed consent and the study was approved by the Local Ethical Committee and conformed to the Declaration of Helsinki on human research. (World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000;284:3043–3045).

In particular, concerning the data we are going to analyze in this paper, following previous publication [33], we briefly describe the acquisition procedure. In the morning, after an overnight fast, all patients were submitted to routine coronary angiography and definitively enrolled after excluding the presence of significant coronary stenosis. Measurements of coronary perfusion pressure, flow velocity, and cross-sectional area in the proximal third of the left anterior descending (LAD) were performed at completion of diagnostic coronary angiography. A 6F guiding catheter was placed in the left main coronary ostium through a 7F femoral artery introducer after an intracoronary heparin bolus (100 U/kg) was given and, a 0.014-in. Doppler flow wire (FloWire, Volcano Corp.) was advanced into the LAD. A 2.9 F, 10 MHz IVUS catheter (Eye Gold, Volcano Corp.) was passed over the flow wire and positioned in the LAD immediately distal to the first septal perforating branch. The Doppler flow wire was positioned two centimeters distal to the tip of the IVUS catheter to avoid artifact caused by the catheter wake. The position of the IVUS catheter and flow wire was documented by angiography and maintained throughout the study by fluoroscopic control. After calibration, phase and mean coronary perfusion pressure (from the guiding catheter) and coronary flow velocity signals were continuously recorded on paper and acquired, together with ECG (leads I–II–III), on a personal computer equipped with dedicated software. IVUS images were obtained for a time greater or equal than 30 seconds at each step of the protocol, with temporal synchronization with flow velocity signal, and recorded for off-line analysis (see [33] for further details). After the instrumentation was completed (about 30 min), continuous monitoring of coronary hemodynamic signals was started and the baseline measurements were registered (baseline). Afterwards, an intravenous adenosine infusion (140 μg/kg/min) was given for 3 min unless it was not clinically tolerated or significant bradycardia (heart rate < 50 beats/min) or hypotension (systolic blood pressure < 90 mmHg) occurred. Coronary parameters were acquired at the end of the third minute of adenosine administration, or just before suspension, and were used to estimate CFR.

Idiopathic dilated cardiomyopathy is a suitable model for assessing coronary flow rates in a more clean fashion than in ischemic heart disease. Patients with idiopathic dilated cardiomyopathy are known to have impaired myocardial blood flow and coronary flow reserve [34]. These patients have microcirculatory abnormalities reducing the coronary vasodilating capacity, although the epicardial vessels are angiographically normal. Measurements by intracoronary Doppler flow wire technique are not affected by the idraulic effect of stenosis, allowing a better steady state situation during the entire duration of the measurements (basal and vasodilating phase).

Using these data, CFR has been estimated using the parabolic and the Womersley-based formula for the computation of the flow rates, thanks to formula (19).

We observe that no ad hoc data acquisition has been needed in order to evaluate the flow rates (and then the CFR) using the Womersley-based formula. An important feature of this formula is actually that it can be used from data commonly measured in the clinical practice.

As shown in Table 2 and in Fig. 3, Womersley-based formula provides a higher value of the estimate of the CFR (mean value 2.65 ± 0.85), with the respect to the one performed by the parabolic formula (mean value 2.56 ± 0.75), in all the patients but one (patient no. 11). We observe that this patient is the only one such that the Womersley number is smaller under adenosine rather than at rest. This is due to the fact that for this patient heart rate is slower under adenosine than in resting conditions.

Moreover, in Table 2 the values of the flow rate estimated with the parabolic formula (\(\hat{Q}_R\) and \(\hat{Q}_S\)) and with the Womersley-based formula (\(Q_{Rw}\) and \(Q_{Sw}\)) are shown. We notice that Womersley-based formula provides an higher value in all the patients. In particular, the mean value of the flow rate in resting conditions and under adenosine obtained with the parabolic formulas is \(\hat{Q}_R = 1.80 ± 0.44\) and \(\hat{Q}_S = 4.27 ± 1.33\), respectively, while for the Womersley-based formula we obtain \(Q_{Rw} = 1.98 ± 0.49\) and \(Q_{Sw} = 4.89 ± 1.76\).

![Fig. 3 – Estimation of the coronary flow reserve (CFR) obtained with the parabolic and with the Womersley-based formula. (×) Womersley-based formula; (○) parabolic formula. The patients with idiopathic dilated cardiomyopathy (1–8) and the healthy ones (9–13) are separated by the dashed line.](image-url)
At the moment, we do not have accurate measures for a deeper error analysis. We limit ourselves to comment the comparison between our results and the parabolic formula and how they do fit with clinical expectation. As a matter of fact, experience of medical doctors suggests that parabolic formula tends to underestimate flow rate and CFR as we have previously pointed out. Since our results feature a systematic overestimation in comparison with parabolic ones, we consider them fairly promising. A more accurate comparison by using a set of accurate in-vivo measures obtained with PC-MRI is found in [42]. Moreover, in Table 2 the relative differences \( \varepsilon \) between the two CFR estimates are shown. The mean value of \( \varepsilon \) related to the first 8 patients in Table 2 (those with idiopathic dilated cardiomyopathy) is 2.53 \( \pm \) 2.42%, while the mean value in the healthy patients is 3.55 \( \pm \) 4.98%. Because of the small sample size, the two groups are still not well separated.

Data collected so far are just a small sample intended for a preliminary exploration and not for building a statistically significant data set. Starting from these promising results, we plan to enlarge our data base, in particular including cases with high Womersley number, namely those observed in vessels with larger diameter than that of coronary arteries. In fact, in the present study, formula (6) was applied to arterial vessels with small Womersley numbers (namely in the range 2.07–4.00). As shown in [40], formula (6) should further improve accuracy of CFR calculation when applied to clinical conditions characterized by higher values of the Womersley number, such as for elevated heart rates, as during atrial pacing tachycardia.

A sensitivity analysis of this formula on the diameter and maximum velocity measures quantifies the errors affecting the flow rate estimate due to measurements errors of diameter and velocity. Parabolic formula is in general less sensitive to this kind of errors, being in general less sensitive to the hemodynamic conditions of the patient. However, we have shown that the increment in sensitivity of the Womersley-based formula is not significant when the Womersley number is \( W < 2.7 \) or \( W > 3.1 \). On the contrary, for intermediate Womersley numbers, original formula is remarkably more sensitive to these errors. Consequently, we modified the formula proposed previously in a way that reduces the sensitivity to 38% more than the parabolic formula versus 68% of the original one.

A first preliminary clinical application of the Womersley-based formula has been provided too. We considered a catheter-based Doppler velocimetry analysis for the measurements of the CFR. We have compared flow rate and CFR estimates provided by both parabolic and Womersley-based formula. Estimates of flow rates provided by the new formula are always greater than the ones given by the parabolic one. The same situation occurs for the CFR apart from one patient. These results have suggested that the new formula is more accurate in view of the clinical evidence of a bias of the parabolic formula, that tends to underestimate CFR and flow rate. Obviously, other Doppler-based techniques could in principle improve the estimation of the flow rate as well.

We point out that the Womersley-based formula does not require specific \textit{ad hoc} measurements procedures and it is therefore readily applicable in single-point Doppler measures. A specific \textit{in vivo} validation comparing the estimates provided by the new formula with accurate flow rate measures obtained by PC-MRI (referred to as the gold standard technique) is presented in [42].

5. Conclusions

In this paper we have analyzed the estimation of the blood flow rate at the peak instant based on available measures of the maximum velocity obtained by the single-point Doppler technique which is used extensively in clinical practice. In particular, we have considered the formula proposed in [40] (called Womersley-based formula) which is able to incorporate data on the blood pulsatility (by means of the Womersley number \( W \)).

### Table 2 – Flow rates and coronary flow reserve (CFR) estimated with the parabolic formula (3) and with the Womersley-based formula (6), from the data collected at the Centro Nazionale delle Ricerche (CNR)—Clinical Physiology Institute, Pisa, and relative difference \( \varepsilon = (\text{CFR based on (6)} - \text{CFR based on (3)}) / \text{CFR based on (6)} \).

<table>
<thead>
<tr>
<th>Patient</th>
<th>( W ) basal/adenosine</th>
<th>( Q_w^b ) (cm(^3)/s)</th>
<th>( Q_w^d ) (cm(^3)/s)</th>
<th>( Q_w^m ) (cm(^3)/s)</th>
<th>( Q_p^w ) (cm(^3)/s)</th>
<th>( \text{CFR}_p ) based on (3)</th>
<th>( \text{CFR}_w ) based on (6)</th>
<th>( \varepsilon )</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2.88/3.19</td>
<td>1.73</td>
<td>6.50</td>
<td>1.93</td>
<td>7.83</td>
<td>3.75</td>
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<tr>
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### Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.
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