ABSOLUTE BLOOD FLOW MEASUREMENTS: PRINCIPLES

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PROBLEMS WITH ABSOLUTE FLOW (and FLOW VELOCITY)

• *absolute blood flow* has no meaning without knowledge of the extent of the perfusion area or without knowing a normal value.

• Absolute flow and all *flow-derived parameters* are dependant on perfusion pressure, which is highly variable within the same patient.

• *Coronary* blood flow is often not representative for *myocardial* perfusion, especially not in case of severe stenosis.

• Coronary flow, velocity, and CFR do not discriminate *epicardial or microvascular disease*.
Consequently, for *routine interventional practice* and decision making in the catheterization lab, absolute flow or flow velocity has little value.

*Fractional Flow Reserve (FFR)* perfectly describes the influence of the epicardial stenosis on myocardial perfusion.

For *scientific purposes* and assessing the *microcirculation*, things might be different.
If you know absolute maximum blood flow in ml/min for an arbitrary stenosis, arbitrary myocardial distribution and any blood pressure and heart rate (e.g. 80 ml / min)

AND you know FFR (e.g. 0.50)

you also know the normal maximum flow for that respective distribution under those specific hemodynamic conditions:

⇒ 160 ml / min (!)
...and if you also know *coronary wedge pressure* (Pw), you know both the absolute myocardial, coronary, and collateral flow

*(because FFR gives the relative contribution of coronary arterial and collateral flow to myocardial flow)*

...and if you measure *coronary pressure* simultaneously, you know *all resistances quantitatively* for any arbitrary coronary segment, myocardial distribution, or collateral bed.

*Easy assessment of microcirculation and collaterals*
So, from the scientific and physiologic point of view, it would be attractive to measure hyperemic absolute flow (in conjunction with pressure)...

- assessing the microcirculation
- quantitation of collateral flow
- quantitation of microvascular flow and resistance in specific patient groups:
  - heart-transplant follow-up
  - stem cell therapy
  - syndrome X (whatever it might be)
  - prognostic stratification after STEMI
continuous infusion of saline to determine absolute maximum coronary blood flow
saline infused at 20 ml/min
temperature of saline is 5° below blood temperature
after mixing, temperature of mixture is 1° below blood temp

blood flow must be 5 x infusion flow of saline
Absolute max coronary blood flow

\[ Q_b = Q_i \cdot \frac{T_i}{T} \cdot 1.08 \]

- Temp of infusion at tip of guiding catheter
- Temp of blood at sensor position

Saline infused at 20 ml/min
Temperature of saline is 5° below blood temperature after mixing, temperature of mixture is 1° below blood temp

Blood flow must be 5 x infusion flow of saline
continuous infusion of saline to determine absolute maximum coronary blood flow

**Prerequisites:**

- decrease of coronary temperature should be large enough to be detected and stable (or stated another way: temperature sensor should be sensitive enough to detect changes), given a reasonable injectate flow (**adequate signal/noise ratio**)

- **complete mixing** of blood and saline between injection site (= tip of infusion catheter) and sensor position

- **heat ("cold") loss through the wall** of the artery must be small compared to convection by blood
Animal study:
instrumentation
ANIMAL STUDY: methods

- five mongrel dogs, 28-43 kg
- instrumentation of LCX by perivascular flow probe and perivascular balloon occluder at day 0
- cardiac catheterization at day 7, Amplatz guiding catheter
- 0.014” pressure wire (RADI) distal to flow probe/occluder for coronary pressure & temperature measurement
- 2.8 F special infusion catheter (AMT, Inc) over wire, position just proximal to occluder
- creation of different degrees of stenosis (corresponding with FFR of 0.85, 0.70, 0.55, 0.40)
- measurements with continuous saline infusion at 2 different infusion rates and 2 different sensor positions
- in-duplo measurements for all degrees of stenosis, both infusion rates, and both sensor positions:

$4 \times 2 \times 2 \times 2 = 32 \text{ measurements per dog}$
Infusion Catheter For Thermodilution (Hexacath®)
(complete mixing of blood and saline)

without guidewire

with guidewire
\[ Q_b = 20 \times \left( \frac{-5.27}{-0.85} \right) \times 1.08 = 134 \text{ ml/min} \]
Dog #5

\[ T = -0.85^\circ \]

\[ T_i = -5.27^\circ \]

\[ P_a \]

\[ P_d \]

\[ Q_b = 134 \text{ ml/min} \rightarrow \text{normal max flow} = 100/86 \times 134 = 156 \text{ ml/min} \]
Animal study: results in the individual dogs
Animal study: *reproducibility* (N=72)
Animal study: *high versus low infusion rate*

- 15-25 ml/min
- 8-15 ml/min
- saline room temp
Animal study: *proximal versus distal sensor position*

3 cm vs 6 cm from tip of infusion catheter
Human validation study
Human study:

instrumentation
Patient # 1:

- normal right coronary artery
- Qi = 25 ml / min saline at room temperature
- sensor located 7 cm from tip of infusion catheter
continuous infusion during 3 minutes

Qb = 25 \times \left( \frac{7.1}{0.97} \right) \times 1.08 = 198 \text{ ml/min}

(and normal max flow in this artery is \( \frac{100}{86} \times 198 = 230 \text{ ml/min} \))
Patient # 3:

Before intervention

- stenotic right coronary artery
- $Q_i = 15 \text{ ml/min}$ saline at room temperature
- distance 7 cm

After successful stenting:

- $Q_i = 15 \text{ ml/min}$
- $Q_i$ is 20 ml/min
Male 58-y-old

Stenose proximale RCA
FFR RCA = 0.42

- Sensor at ostium
- Across stenosis
- Hyperemia
Infusion in RCA

At first, Qi=10ml/min, next infusion interrupted and restarted with a rate of Qi=15ml/min.

\[ T = -1.26 \]
\[ T_i = -5.36 \]

\[ Q_b = 15 \times (5.21 / 1.31) \times 1.08 = 64 \text{ ml/min} \]
After stenting of RCA: FFR=0.98

Infusion rate Qi = 15ml/min.

Qb = 15 x (5.5 / 0.45) x 1.08 = 196 ml/min
**Human Study: Selected Patients**

- 35 patients referred for PCI or FFR measurement

- single stenosis in segment without major sidebranches (24 RCA, 10 LAD, 1 LCX)

- FFR ≤ 0.75 in 14 patients → stenting
  - in these patients thermo measurement before and after PCI with saline at room temperature, for indirect quantitative validation

- in 10 patients 2 different infusion rates of saline (10-15 and 15-25 ml/min)

- in 11 patients 2 different sensor positions (3-4 and 6-8 cm distal to the tip of the infusion catheter)

- all measurement in duplo with 2-min interval in between
**Human study: quantitative validation**

**Measured versus predicted flow**

\[ y = 0.99x - 3.6 \]

\[ R^2 = 0.91 \]

**Bland Altman calculated vs predicted %**

**Actual measured flow** vs **predicted flow**

\[ y = 0.99x - 3.6 \]

\[ R^2 = 0.91 \]
Human study: reproducibility

Reproducibility

\[ y = 1x + 0.93 \]
\[ R^2 = 0.97 \]

Bland Altman reproducibility %

Relative difference \( Q_{\text{calc}1} \) and \( Q_{\text{calc}2} \) [%]
Clinical application:

Absolute Myocardial Flow and Microvascular Resistance in Acute Myocardial Infarction and at Follow-up

Wijnbergen et al, submitted
absolute flow in the infarct area (ml/min/g)

hyperacute phase day 5

absolute resistance in the infarct Area (dyn.s.cm^{-5})

Figure 4a

Figure 4b
\[ Q_b = 1.08(T/T_i)^*Q_i = 1.08(-7.95/-1.07)*20 = 160 \text{ ml/min} \]
HUMAN STUDY: CONCLUSIONS (1)

• Using this technique of continuous low rate saline infusion, direct measurement of absolute coronary blood flow is possible.

• Within reasonable limits, the measurements are independent of infusion rate and sensor position.

• Use of a specific infusion catheter (Hexacath, Inc, Paris) ensuring complete mixing, is paramount.

• Because pressure is measured simultaneously, also coronary resistance can be calculated quantitatively.

• When Pw is also measured (and FFR_{myo}, FFR_{cor}, and FFR_{coll} are known) also absolute microvascular flow and resistance and absolute collateral flow and resistance can be calculated.
NOTES:

• Very reproducible, not difficult, some patience required

• Instrumentation (introduction and connection of the infusion catheter) is not trivial and needs to be done carefully

• The infusion catheter is not commercially available yet; monorail infusion catheter is underway *(hexacath, Paris)*

• In my view, the method is useful for scientific purposes and very specific categories of patients, (post-HTX, syndrome X, microvascular disfunction, AMI) and can be used by dedicated interventionalists in the cathlab
**Human study: proximal vs distal sensor position**

- **Influence of position of sensor**
  - Regression equation: $y = 0.99x + 3.4$
  - $R^2 = 0.94$

- **Bland Altman for different positions %**

- **Proximal position (3-4 cm)**
- **Distal position (6-8 cm)**
Human study: low vs high infusion rate

Influence infusion rate

\[ y = 1.1x + 9.4 \]
\[ R^2 = 0.87 \]

Bland Altman different inf rates %

Relative difference \( Q_{\text{calc}} \), different inf rates [%]

Mean \( Q_{\text{calc}} \) for different inf rates [ml/min]

low infusion rate 10-15 ml/min

high infusion rate 15-25 ml/min
tip of the guiding catheter

infusion catheter

tip of the guiding catheter

sensor of the radiwire
Stenotic LAD artery, FFR = 0.69

Qb = 4.5/0.9 * 15 * 1.08 = 81 ml/min
Male, 56-y-old

Fladderak
PatID: <17094898016>
W: 175 L: 140
XA 57/73
Qb = \( 25 \times \left( -\frac{7.1}{-0.97} \right) \times 1.08 = 198 \, \text{ml/min} \)
The dream of every cardio-scientist would be to know

- coronary, myocardial, and collateral blood flow quantitatively

and

- to be able to relate such values to the normal values for that individual patient!!

Together with distal coronary pressure measurement, this would also enable the calculation of

- true (absolute) microvascular resistance

enabling studying microvascular disorders, evaluation of stem-cell therapy, and many others
Or vice-versa:

- FFR after stenting is $0.98 = 160\text{ml/min}$
- $160\text{ml/min} = 98\%$
- $164\text{ml/min} = 100\%$

- FFR before stenting was 42\%
- This correlates with $164 \times 42\% = 69 \text{ml/min}$, whereas we found 69 ml/min by the first “direct” measurement
So, for clinical decision making in the cathlab, absolute flow has little value.

Besides that, it has been impossible so far to measure absolute coronary or myocardial flow invasively.
pressure ($P_d$) (mm Hg)

flow (Q) (ml/min)

AORTA
100 mmHg
During Maximal Vasodilatation

\[ FFR_{myo} = \frac{P_d}{P_a} = 0.70 \]
Pressure-flow equations:

1. Fract. Myocardial Flow Res. \[ (\text{FFR}_{\text{myo}}) = \frac{P_d - P_v}{P_a - P_v} \]

2. Fract. Coronary Flow Res. \[ (\text{FFR}_{\text{cor}}) = \frac{P_d - P_w}{P_a - P_w} \]

3. Fractional Collateral Flow \[ = \left( \text{FFR}_{\text{myo}} - \text{FFR}_{\text{cor}} \right) \]

\( P_a = \) mean aortic pressure at maximum hyperemia
\( P_v = \) mean central venous pressure at maximum hyperemia
\( P_d = \) mean distal coronary pressure at maximum hyperemia
\( P_w = \) coronary wedge pressure at balloon inflation

*Circulation* 1993;87:1354-1367
17 vb5-PTCA - de Wit-Stek (8)
# Example (1)

<table>
<thead>
<tr>
<th></th>
<th>before PTCA</th>
<th>occlusion</th>
<th>after PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pa</strong></td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td><strong>Pd</strong></td>
<td>40</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td><strong>Pv</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Pw</strong></td>
<td>-</td>
<td>20</td>
<td>-</td>
</tr>
</tbody>
</table>

\[
\text{FFR}_{\text{myo}} = \frac{40-0}{90-0} = \frac{80-0}{90-0}
\]

\[
\text{FFR}_{\text{cor}} = \frac{40-20}{90-20} = \frac{80-20}{90-20}
\]

\[
\text{collateral flow at occlusion} = \frac{20-0}{90-0} = 0.22
\]
## Example (1)

<table>
<thead>
<tr>
<th></th>
<th>before PTCA</th>
<th>occlusion</th>
<th>after PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>fract. myoc. flow res.</td>
<td>0.44</td>
<td>0.22</td>
<td>0.89</td>
</tr>
<tr>
<td>fract. coron. flow res.</td>
<td>0.29</td>
<td>-</td>
<td>0.86</td>
</tr>
<tr>
<td>fract. collat. flow</td>
<td>0.15</td>
<td>0.22</td>
<td>0.03</td>
</tr>
</tbody>
</table>
...and it would even be more attractive if absolute flow and resistance could be related to a normal value for an individual patient and individual heart rate, blood pressure, etc!
In-vitro tests:  

- $o = $ BS modified & OCCAM-2 infusion catheter
- $x = $ standard infusion catheter

* incomplete mixing $\rightarrow$ underestimation of flow
ANIMAL STUDY: CONCLUSIONS

• Using this technique of continuous low rate saline infusion, direct measurement of absolute coronary blood flow is possible.

• Within reasonable limits, the measurements are independent of infusion rate and sensor position.

• Use of a specific infusion catheter ensuring complete mixing, is paramount.

• Because pressure is measured simultaneously, also resistance can be calculated quantitatively.

• The method can be extrapolated to man without major modifications.
FFR before stenting = 0.42

Qb before stenting = 69 ml/min

\[ \text{Expected normal max flow} = \frac{100}{42} \times 69 = 163 \text{ ml/min} \]
FFR before stenting = 0.42
Qb before stenting = 69 ml/min

→ Expected normal max flow = $\frac{100}{42} \times 69 = 163 \text{ ml/min}$

FFR after stenting = 0.98
Qb after stenting = 160 ml/min

→ “true” normal max flow = $\frac{100}{98} \times 160 = 164 \text{ ml/min}$
Traditional coronary sinus thermodilution:

- disappointing results, not suitable for clinical use
- not specific for one coronary artery or branch
- could not be related to a normal value
- grossly inaccurate due to **incomplete mixing:**
  - design of infusion catheter
  - venous vs pulsatile arterial flow
  - entangling of saline along catheter
Human Study: Measurement protocol

- introduction of pressure wire
- hyperemia by i.v. adenosine 140 µg/kg/min
- measurement of FFR, stop adenosine
- introduction of infusion catheter over PW
- connection of infusion catheter to infusion pump by second Y-connector
- induction of steady state hyperemia by i.v. adenosine 140 µg/kg/min
- at steady state hyperemia: zeroing of blood temperature
- start saline infusion (room temp; 10-25 ml /min = Q_i) results in rapid decrease of distal blood temp by 0.5-2.0 °C
- recording of steady state during 20-30 seconds (T)
- rapid withdrawal of PW to record infusion temperature (T_i)
- stop adenosine; repeat sequence 2 min later
myocardial blood flow = coronary flow + collateral flow

FFR myo = FFR cor + FFR coll

Before PCI (stenotic artery) : 0.44 = 0.29 + 0.15

After PCI (stented artery) : 0.89 = 0.86 + 0.03

So, myocardial, coronary, and collateral flow both before and after PCI, are all expressed as a fraction of **normal maximum myocardial blood flow**

→ If one of these numbers is known quantitatively (ml/min), all the other values are known as well

→ And if distal coronary pressure is also measured, microvascular resistance is known as an absolute number
FFR describes the mutual relation between:

- Myoc flow in stenotic artery
- Myoc flow in normal artery
- Coronary flow in stenotic artery
- Coronary flow in normal artery
- Collateral flow in stenotic artery
- Collateral flow in normal artery
- Microvascular resistance under different circumstances
- Coronary resistance in stenotic artery
- Coronary resistance in normal artery
continuous infusion of saline to determine absolute maximum coronary blood flow

\[ Q_b = Q_i \cdot \frac{T_i - T_b}{T - T_b} \cdot 1.08 \]

And if all temperatures are expressed relative to the Temperature of the blood (zero-ed):

\[ Q_b = Q_i \cdot \frac{T_i}{T} \cdot 1.08 \]

Absolute max coronary blood flow

infusion flow
OCCAM/AMT infusion catheter design:
- 2.8 F outer diameter
- 4 sideholes in last 8 mm
- almost no infusion through tip
- maximum infusion 40 ml/min
continuous infusion of saline to determine absolute maximum coronary blood flow: theory

- Temperature sensor somewhere in the distal part of the coronary artery
- Induction of steady state hyperemia (i.v. adenosine)
- Measurement of blood temperature ($T_b$)
- Infusion of saline with known infusion rate ($Q_i$) and known temperature ($T_i$)
- Measurement of temperature of sensor ($T$) after mixing of blood and infused saline
- Calculation of maximum absolute flow ($Q_b$) by:

$$Q_b = \frac{T_i - T_b}{T - T_b} \cdot Q_i \cdot 1.08$$

Zierler, 1954
Ganz, 1971
After stenting of RCA: FFR = 0.98
Infusion with Qi = 20 ml/min.

Qb = 20 x (6.9 / 0.83) x 1.08 = 160 ml/min