Quantitative Gated Intravascular Ultrasound Largely Reduces the Population Size for Atherosclerosis Progression-Regression Trials: A Computer Simulation Study

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Abstract

During imaging of coronary vessels with ultrasound (ICUS), cardiac cycle-dependent motion of the catheter introduces artifacts resulting in possible measurement inaccuracies. Although this problem can be avoided by ECG- or image-based gating, still most analyses are performed non-gated in longitudinal studies investigating the effects of new interventional methods on coronary atherosclerosis progression-regression.

To investigate the impact of these motion-induced artifacts on the possible outcome of these studies, we developed a computer simulation model. In the model a clinical trial (n=400) was simulated where 200 patients received a drug (estimated 3% plaque reduction) and 200 a placebo.

Using gating the 3% plaque reduction could be detected in 26 patients while for non-gated analyses 254 patients were necessary, indicating that gating can reduce population sizes significantly.

1. Introduction

Intracoronary ultrasound (ICUS), with its excellent capabilities to show atherosclerotic plaques, has become the de-facto standard to evaluate new interventional techniques[1,2]. Quantitative parameters derived from ICUS (QCU) are often used as primary and/or secondary endpoints for atherosclerosis progression-regression studies. The ICUS catheter, advanced through a sheath, generates a sequence of planar images, which are sequentially recorded during an automated pullback procedure operating mostly at a slow constant speed of 0.5 mm/s[2]. This structured imaging of the coronary vessel enables the possibility to create a three-dimensional (3D) reconstruction (also called longitudinal views (L-views)), which can present a comprehensive overview of structures in the coronary vessel wall. It also makes it possible to perform quantitative analysis[3], where the L-views can help to locate landmarks necessary to identify vessel segments acquired at different time points in longitudinal studies.

Typical measured coronary dimensional parameters are lumen- and vessel areas from which the plaque area (vessel − lumen) is calculated[2]. Areas multiplied by length result in plaque volumes. The change in plaque is mostly used to evaluate the effects of new drugs and interventional techniques. However, since the heart is a highly dynamic organ, systolic-diastolic variations in vessel dimensions[4] along with the cyclic movement of the catheter in the coronary arteries throughout the heart cycle[5,6] introduce a strong dependency of the appearance of an image frame (e.g. its anatomical orientation) in the imaging sequence on the phase of the heart cycle. Both the dimensions of the vessel wall itself and the longitudinal as well as transversal position of the catheter in the coronary at a certain time lead to an inconsistent and almost always incorrect representation.

The effects of these artifacts can be minimized by the application of cardiac phase gating such as retrospective image-based gating and prospective ECG gating. This method eliminates the aforementioned problems and several studies reported the effects for both visualization and quantitative analyses[5,7-9]. Although multiple gating solutions have been reported, there is still an on-going debate about whether gating results in significant different quantitative study outcomes over non-gated analyses.

We hypothesized that a computer simulation study investigating the aforementioned influence of coronary dynamics and cyclic catheter motion for QCU analysis could help to understand the underlying mechanism and possible effect of gating on the analysis results.

2. Methods

2.1. Coronary model

The parameterization of the software simulator is based on information derived from real-life longitudinal atherosclerosis progression-regression studies[8]. Choice of diameters and lengths for each segment was determined based on their mean values of the vessels used in these studies.

All vessels were modeled as 3D tapered cylindrical bodies (tubes), to match the decreasing vessel diameter towards the distal end. The lumen was also modeled tapered and parallel to the vessel border. Plaque was introduced at random locations as local enlargements of the outer vessel diameter over a randomly chosen length, according to findings in real-life pullbacks[8]. In absence of catheter motion, pullbacks would be simulated as shown in figure 1, where a virtual catheter is advanced from the distal to the proximal end measuring increasing diameters. Presence of plaque causes local diameter increments.

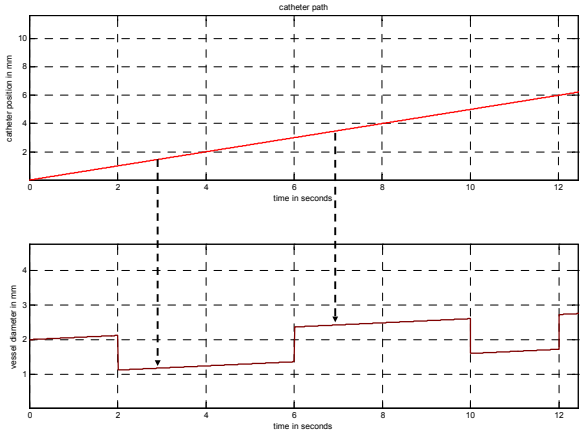

Figure 1. Simple representation of a linear coronary pullback where vessel diameters change over time.

2.2. Simulation of catheter motion

Motion was introduced by describing the positions of the catheter path over time with piece-wise quadratic functions instead of the linear function in figure 1. This adequately models the sweep of the catheter tip that appears as a repetitive longitudinal displacement in every heart cycle. Figure 2 illustrates the actual catheter position over time compared to the linear path aimed at while performing the pullback. The star-shaped markers indicate the positions where images are acquired if conventional ICUS analysis using slices 0.5 mm apart is performed. This clearly differs from the linear path.

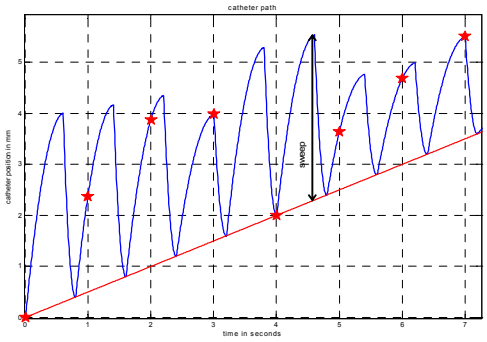

Figure 2. The modeled catheter path over time shows the actual distance of the catheter tip from the distal origin.

Applying the model of the catheter motion onto coronary models like the one described in figure 1, gives information on the measured vessel diameter at any point in time during a (virtual) pullback. The measured diameters now differ in a way that is hard to predict from figure 1. In figure 3 the lower panel shows both the linear sequence and the one after introducing the catheter motion. The appearance of the latter can be constructed from the linear path using point translation as follows (figure 3):

a) The position at any point in time corresponds to a point on the linear path later in time (arrow 1).
b) The vessel diameter on the linear path that belongs to this point is found from arrow 2.
c) Due to the presence of the catheter at this point earlier in time, this vessel diameter will also appear earlier and hence will be translated along arrow 3.

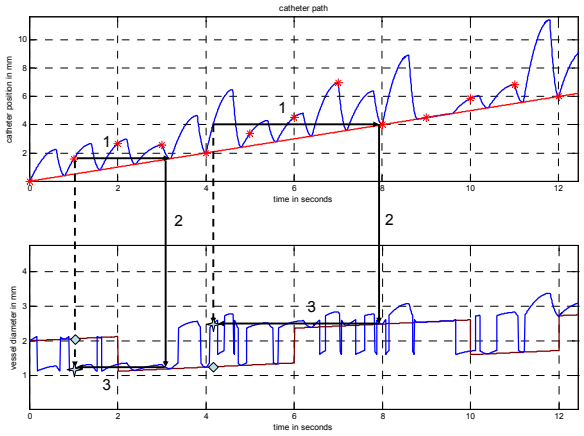

Figure 3. Point translation of the vessel diameters in the model describe the diameters as measured 'in-vivo' with moving catheter resulting from cardiac motion.

2.3. ICUS progression-regression study simulation

A simulated study contained 400 individually modeled patients. Half of this population received treatment which exactly reduced the plaque volume by 3% and the other half a placebo which left the plaque unchanged.

The longitudinal catheter motion was set to range between 0 and 5 mm[6], with a skewed distribution having a mean of 1.25 mm. Heart rate was set to a random value from a normal distribution with average 72±10 BPM. Cyclic vessel area changes as a result of coronary pulsation were taken in a range of 10% per cardiac cycle [4,10]. The pullback speed was assumed to be 0.5 mm/s and the imaging rate 30 fps. Vessel radius was ranging from 1.83mm±0.74 mm distal to 2.62±0.65 mm proximal and all these parameters are adopted from real clinical trials[6,8].

After introducing the virtual plaque decrease in the treated population the simulation was repeated with different values for the heart rate, coronary pulsation and catheter sweep to form the follow-up data set. The volume differences were calculated using three methods: 1) calculation of the exact volume (simulated golden standard); 2) conventional non-gated QCU analyzing one ICUS cross-sectional image at 0.5mm distances (or 1s in time) and 3) image-based gated QCU. For all three methods a two-tailed paired student's t-test was performed.

To find out how many patients need to be included in this test to assure a significantly different population and hence detect the effect of the treatment, all possible combinations of subpopulations N_{sub} each with an equal number of treated and placebo patients were evaluated. The required number of patients n_r follows from:

$$n_r = \min (N_{sub} \mid N_{sub} \geq 10, p < 0.05),$$

with p the p-value of the t-test. A value of N_{sub} below 10 is assumed too small to perform a t-test.

The entire simulation experiment was performed 150 times to simulate an equal number of independent clinical trials.

3. Results

After 150 simulations, treatment effect of 3% decrease was detected in all patients for method 1 ($p<0.05$) with $n_r=10$. Method 2 detected significant change only after inclusion of 254 patients ($n_r=254$). Method 3 detected significant change after inclusion of 26 patients ($n_r=26$). Measured volumes for each method (m1, m2, m3) are displayed in table 1.

Mean segment length in all studies was 38±12 mm and vessel diameters ranged from 3.5 mm to 5.7 mm. Mean longitudinal catheter shift was 2.6±1.3 mm.

Analysis	Placebo (mm^3)	Treated (mm^3)	p
m1 (base)	606.7±368.2	542.9±301.2	0.06
m1 (fup)	606.7±368.2	526.6±292.1	0.02
m2 (base)	649.6±388.6	586.3±320.7	0.06
m2 (fup)	653.2±392.2	571.6±312.5	0.02
m3 (base)	614.9±373.5	551.3±306.2	0.08
m3 (fup)	614.9±373.5	534.0±296.8	0.02

Table 1. Measured volumes at baseline (base) and follow-up (fup) for all three methods (see 2.3) and p-values.

4. Discussion and conclusions

This study shows that neglecting the cardiac dynamics in relation to quantitative coronary ultrasound results in different outcomes (table 1). The results of this mathematically simulated phantom study is in-line with previously reported simulations and in-vivo studies, which showed similar differences for mean measured volumes of approximately 5-6%[5,10]. Dhawale et al.[10] focussed on optimal data acquisition for ICUS with as primary finding the application of a low pullback speed (<1.2 mm) and concluded that accurate volumetric plaque analysis requires cardiac phase gating in ICUS imaging. Most problems indicated in this particular study, concerning pullback speed and the application of pro- or retrospective gating have been solved today[5,7,9]. Bruining et al.[11] reported significantly larger vessel- and lumen volumes as measured by prospective ECG-gated QCU, which is in-line with the findings in this study. In addition to these two studies, this study shows that the deviation between non-gated QCU and "reality" is not a systematic difference, which could be accounted for in later statistical analysis, but a random difference with possible large deviations of more than 20%. Figure 4 shows that changes in the parameters can have a large effect on the reported volumes if gating is omitted. This must be taken into account in ICUS driven progression-regression studies were the differences may be potentially small and inter- and intra-observer variability introduced differences obscure the true underlying mechanisms even more.

Both the simulation as well as in-vivo comparison between gated and non-gated QCU is limited. The in-vivo studies due to inter- and intra-observer induced variabilities and a simulation study due to the limited number of phantoms while in-vivo coronary vessels can have an indefinite number of morphologies. Therefore, we simulated a study using a mathematical model and the

aid of a computer in which the segment lengths, vessel shape, coronary pulsation, heart rate and catheter motion were randomly generated within realistic parameter ranges derived from a real-world ICUS driven progression-regression study[8].

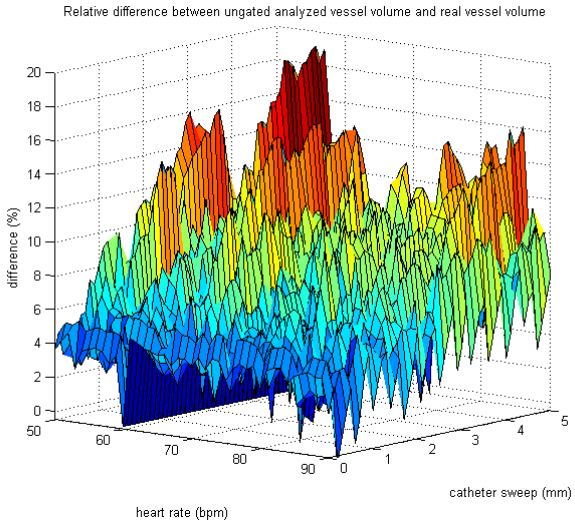

Figure 4. Varying heart rate and catheter sweep introduce large variability in measured volumes if they are compared to the real physical volumes.

The model of the vessel is implemented as a tube that can be configured to contain plaque at various locations. Parameters for the dimensions can be adjusted to accommodate several locations in the coronary tree. Together with the simulated catheter path it is possible to produce an artificial image sequence that can be used to calculate quantitative parameters. In contrast to a real vessel segment, the difference in dimensions can be compared to known vessel dimensions as both are the result of a simulation experiment. In reality the motion characteristic is not accurately reproducible to compare several pullbacks and examine the effects. Even every heartbeat is unique and so are pullbacks.

Even under the simplified, but perfect conditions of this simulation study, with a treatment effect of exactly 3% in all patients, it shows that by applying gating population sizes can be largely reduced over non-gated QCU approaches.

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