True AI Implementation Through FMTVDM Proprietary Equations and QCA

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Introduction

The currently used definition of artificial intelligence (AI) or machine learning (ML) is excessively fluid indicating that few people truly have a solid definition of what is being talked about. While many people have been assembling lists of qualitative tests (yes/no), from which the probability of being correct about the presence or absence of disease, to form their AI, the reality is this is nothing more than a collection of flawed tests designed to answer yes you most likely have disease or no, you most likely don’t have disease. This qualitative guesstimate is not AI. Disease is not an all or none phenomena but rather a continuum [1,2] as genetic and environmental factors interact. Thus, to develop true AI requires the ability to accurately, consistently and reproducibly measure these transitional changes; not only for diagnostic purposes but also for assessment of treatment response. Quantitative coronary arteriography (QCA) [3-6] provides an absolute measurement of the extent of coronary artery disease, defining percent diameter stenosis (% DS) in two orthogonal views, percent area stenosis (% AS), absolute length of lesion, entry and exit angles, density data and measured flow reserve. Flow reserve has been labeled both as coronary flow reserve (CFR) and stenosis flow reserve (SFR), which are the same value which merely differentiate for the uninitiated whether a coronary lumen narrowing exists or not.

The reliability and reproducibility of Automated QCA has been determined using phantoms and clinical studies, providing an accuracy of ± 0.1 millimeter [4-11]. Limitations in the value of visual
qualitative interpretation of coronary arteriograms have been compared with automated quantitative coronary arteriography [4]. While it is possible to reduce, although not eliminate, the human error introduced into qualitative interpretation of coronary arteriograms [12], coronary artery disease itself is not merely a narrowing of a coronary artery but rather a limitation in the ability of the artery to maximally dilate when needed to enhance coronary blood flow; aka. reserve [13]. The limitations of qualitative evaluations of coronary artery disease (CAD) have been well established [14-17]. Despite certain limitations that may affect QCA (distal lesions, inadequate contrast, poor image quality, overlapping vessels, vessel angulation), QCA has become a useful tool in detecting subtle changes in coronary atherosclerosis [3-11].

When used in conjunction with The Fleming Method for Tissue and Vascular Differentiation and Metabolism (FMTVDM), absolute quantification of the extent of CAD can be derived from FMTVDM through the use of proprietary equations, CFR derived [18-24] and corrects the errors originally made in SFR-%DS using dog models [8,25]. Given the interest in the development of AI to improve both diagnostic evaluation and assessment of treatment responses, it is critical that we recognize that true AI is the development of a system, which is not qualitative and is not based upon probabilities but rather absolute quantitative measurements against which clinical decisions can be made.

The validation of FMTVDM has been well established elsewhere (patent # 9566037) in the medical literature, inter alia references [18-24]. To determine if true AI/ML can occur through the exchange of measurements made by two different machine methods, viz. FMTVDM and QCA, we need to know that the exchange of data between these machine systems represent accurate, consistent and reproducible results. Prior QCA studies have only looked at the reproducibility of QCA on phantom images and have not closely examined the clinical variability associated with nondiscrete, eccentric lesions occurring in coronary lumens, which are not straight. This study investigates the parameters and variability associated with automated quantitative coronary arteriography and compares percent diameter stenosis with stenosis flow reserve. If we can guarantee the validity of the QCA measurement system, then the proprietary equations so derived and used with FMTVDM, provide a true means for the two machine methods teaching each other, thereby increasing diagnostic and therapeutic accuracy, devoid of human intervention and error.

Methods

Data Acquisition and Analysis

Data acquisition from diagnostic studies was performed following applicable Institutional Review Board approval and informed consent [3-6]. Acquisition, analysis and consequential data development were done independently and without financial support.

Coronary Arteriogram

One thousand and forty (1040) coronary arteries were analyzed using an automated QCA [3-6]. The stenoses lesions were analyzed by one of two currently available techniques, which have been previously validated [3,4,7,8,25]. All lesions were analyzed for stenosis flow reserve (SFR), as well as percent reduction of diameter and the other parameters mentioned supra.

Automated Quantitative Coronary Arteriography (QCA)

Two previously validated QCA systems were employed in the analysis of each coronary arteriogram. The first system as previously described [3,4,7,8,25] obtained images from biplane views using a Philips Poly Diagnost C/Lateral ARC system with pincushion and magnification correction as described by Brown [10]. End-diastolic cine frames were then selected and digitized by a Spatial Data System frame grabber using a 640 by 480 matrix. The image processing (border recognition, magnification correction and stenosis morphology determinations) was carried out on a DEC VAX 11/780 mainframe computer with hardcopy reporting generated on a Textronics 4207 graphics terminal. The second QCA validated system [9] also utilized end diastolic cine frames using a high resolution (2048 by 3072 pixel) charged coupled device (CCD) to digitize images, which were processed and stored on an Apollo DN 3000 computer workstation.

Statistical Analysis

Percent diameter stenosis (%DS) and SFR were each analyzed for mean + standard deviation and coefficient of variance. SFR was plotted against percent reduction in diameter. Coefficient of variance was plotted against the mean values for % DS and SFR. SFR and % DS were then analyzed for variability and depicted graphically. Using the coefficient of variance for percent diameter reduction (% DS) based upon SFR, the variability of percent diameter reduction was calculated using a three-millimeter example artery.

QCA TO FMTVDM Results

Figure 1 shows the relationship between SFR and % DS and percent area stenosis (% AS). Prior publications [8,25] incorrectly defined the relationship between SFR and % DS based upon the dog model. In humans the % AS to SFR model matches the dog % DS to SFR model. It has previously been shown that what clinicians report as % DS, is actually % AS, which matches density data [4,12] and while this can be improved upon with additional training [12], the use of visual interpretation of coronary arteriograms is still flawed and inferior [13-17] to this AI method of QCA-FMTVDM measured CAD. As [26] Figure 1 shows, there is no appreciable decrease in stenosis flow reserve until a 15 - 20 percent reduction in lumen diameter is present. For the most part, SFR remains in the 4 to 5 region until % DS reaches 35 to 40 percent, explaining why there is a delay in angina symptoms in many people whose inflammatory plaques have already impaired arterial function but have not yet impeded resting lumen flow. Consequently, this model explains why so many people experience myocardial infarctions from plaque rupture with no prior anginal warning signs. FMTVDM can measure these changes in flow reserve by measuring quantitative changes in isotope redistribution unmasking vulnerable plaques through isotope wash-in [18-24]. FMTVDM proprietary equations
using this method provide SFR results obtained using automated QCA as shown in Figure 2 [18,26]. As shown in Table 1 and Figure 3, there is a curvilinear relationship (R = 0.98) between the mean % DS and the mean SFR. Table 2 and Figure 4 further reveals how SFR decreases as the %DS increases, without any apparent increase in the standard deviation of stenosis flow reserve measurements. Figure 4 also reveals an almost linear relationship between SFR and %DS once the lumen narrowing exceeds 50 %DS, with critical reductions in SFR seen when % DS exceeds 70 percent.

Figure 1: Comparison of Percent Diameter Stenosis with Stenosis Flow Reserve [26]. The relationship between both percent diameter stenosis (% DS) and percent area stenosis (% AS) and coronary (stenosis) flow reserve are different curvilinear functions. Prior studies [8,25] using a dog model incorrectly defined the % DS relationship to SFR in humans as the % AS relationship. This is due to the differences in SFR seen between species (canine vs. human). The correct relationship is shown in blue, while the actual % AS for humans is shown in red. In humans there is no appreciable decrease in SFR until a 15-20 percent reduction in lumen diameter exists. While it is not uncommon for clinicians to visually report coronary artery disease (CAD) with % DS greater than 90%, such lesions actually represent changes in % AS [4, 12].

Figure 2: Relationship between QCA derived SFR and the results obtained using FMTVDM (calculated SFR) proprietary equations [18,26]. ML data exchange and enhancement through proprietary equations marks the evolution of AI.
Figure 3: Comparison of Average Percent Diameter Stenosis with Average Stenosis Flow Reserve. When the average values of stenosis flow reserve with error bars of one standard deviation is plotted against the average percent diameter stenosis, there is a strong correlation ($R = 0.98$) between the values obtained.

Figure 4: Stenosis Flow Reserve Based Upon Percent Diameter Stenosis. The results of stenosis flow reserve (SFR) and the respective standard deviations are plotted against the percent diameter stenosis (% DS). There is an inverse relationship between SFR and % DS. There is no appreciable change in the range of variance/standard deviation of SFR calculations whether one is looking at a lesion of ten or ninety % DS.

Table 1: Standard Deviation and Expected Stenosis Flow Reserve Based Upon Percent Diameter Stenosis.

<table>
<thead>
<tr>
<th>Percent Diameter Stenosis</th>
<th>Percent Diameter Stenosis</th>
<th>Stenosis Flow Reserve (standard deviation)</th>
<th>Minimum Stenosis Flow Reserve*</th>
<th>Maximum Stenosis Flow Reserve*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>4.982</td>
<td>0.114</td>
<td>4.868</td>
<td>5.096</td>
</tr>
<tr>
<td>10-20</td>
<td>4.925</td>
<td>0.114</td>
<td>4.811</td>
<td>5.039</td>
</tr>
<tr>
<td>20-30</td>
<td>4.736</td>
<td>0.248</td>
<td>4.488</td>
<td>4.984</td>
</tr>
<tr>
<td>30-40</td>
<td>4.446</td>
<td>0.323</td>
<td>4.123</td>
<td>4.769</td>
</tr>
</tbody>
</table>
### Table 2: Variance of Percent Diameter Stenosis Based Upon Percent Diameter Reduction.

<table>
<thead>
<tr>
<th>Stenosis Flow Reserve</th>
<th>Mean Percent Diameter Stenosis</th>
<th>Percent Diameter (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.99</td>
<td>81.1</td>
<td>3.7</td>
</tr>
<tr>
<td>1.0-1.99</td>
<td>71.4</td>
<td>6.4</td>
</tr>
<tr>
<td>2.0-2.99</td>
<td>61.6</td>
<td>5.9</td>
</tr>
<tr>
<td>3.0-3.99</td>
<td>51.1</td>
<td>6.8</td>
</tr>
<tr>
<td>4.0-5.0</td>
<td>31.9</td>
<td>13.6</td>
</tr>
</tbody>
</table>

### Discussion

Several investigators have previously raised the issue of what constitutes a significant stenosis and how to determine the normal region of an artery from the abnormal regions given the potential of diffusely diseased vessels. Attempts to visualize the normal region by semi-automated quantitative coronary arteriography (QCA) have been one of several approaches employed to try to reduce the error associated with interpretation of coronary arteriograms. However, this semi-automated approach is still associated with the need for human intervention, calibration and a estimations, including determination of the normal proximal region of the artery in question, the location of vessel walls, and determination of the most stenotic region as well as determination of appropriate biplane images when orthogonal views are used. Previously, phantom images with known concentric diameter reductions have been used to examine the reliability of QCA systems and have demonstrated QCA accuracy to within 0.1 millimeter. There are currently no phantoms available with eccentric stenoses and curvatures such as those seen in human coronaries, and the expense of reproducing human coronary arteries from autopsies after previous coronary arteriograms without intervening changes provides not only an economic problem but possibly an ethical one. For this reason, the clinical results from these 1040 coronary arteries, which the primary author has previously analyzed provides the data base against which quantitative conclusions can be drawn with regard to SFR, % DS results and their associated standard deviations. From this, it was possible to provide data, proprietary equations, and a graphical record of the experience to date and its potential use by clinicians.

The theoretical and clinical relationship of SFR to % DS as briefly revealed here shows a curvilinear function where no apparent effect upon stenosis flow reserve occurs until there is at least a 35-40 percent reduction in coronary lumen diameter. This plateaus off at approximately 85-90 % DS. No lesions were quantitatively reported in the range of 91-100 % DS, leading one to suspect that stenoses in this range tend to totally occlude or were not detected on arteriography. These two variables can also be compared as average values obtained over the stenoses studied, yielding a strong (R=0.98) coefficient of variance between the two. This relationship allowed for the development of proprietary equations, which can be used to calculate stenosis flow reserve from percent diameter stenosis, and percent diameter stenosis from stenosis flow reserve, respectively as shown in Figure 2. The development and use of Figure one allows clinicians to estimate the stenosis flow reserve for a given lesion based upon % DS. However, the use of visual estimates of % DS cannot be improved by the simple use of Figure one and likewise, Figure one is only as useful as the accuracy of the method used to determine % DS. Based upon the results obtained by analyzing this SFR data and comparing it with the FMTVDM data, several points can be made. First, a coronary lumen narrowing alone, which has less than a 40 percent reduction in diameter stenosis due to the development of an underlying coronary artery inflammatory plaque [27-32], cannot be appreciably detected using arteriography or QCA analysis. These plaques can be detected using intravascular coronary ultrasound (IVUS) once the clinician knows where to look for them. Such inflammatory plaques are extremely important clinically as they account for the majority of sudden cardiac death seen in individuals with no or few prior anginal symptoms. These plaques are measurable using FMTVDM to unmask the underlying inflammatory plaques and expose their effect upon CFR as detailed elsewhere [1-2,18-24] and provide the necessary information needed by the interventional cardiologist.

Second, lesions with a greater than 40 percent reduction in diameter are associated with linearly decreasing SFR. Third, while lesions with a greater than 85 % DS have the widest variability in SFR, they all are associated with a SFR of < 1.0, revealing impaired coronary flow at rest and a further impaired ability to increase coronary blood flow when needed, thus representing significant and potentially life-threatening CAD. The key to improved diagnostic and therapeutic CAD intervention is contingent upon accuracy. Accuracy is determined by the ability to measure and...
not qualitatively look for the presence or absence of disease. The human eye and brain are unable to define CAD at the level where coronary artery plaques are impairing coronary artery function. Furthermore, the reliability of qualitative imaging is associated with sensitivity and specificity errors already well established in the medical and lay literature; independent of whether we are talking about coronary arteriography or myocardial perfusion imaging (MPI). Quantification of coronary arteriography requires QCA and quantification of MPI requires FMTVDM. The development of proprietary equations (FMTVDM) provides the artificial intelligence (AI) language for these machines to learn from each other as shown in Figure 5. The acquired information from QCA teaches FMTVDM and FMTVDM teaches QCA. The consequential refinement and ML that occurs, will further enhance this quantification of CAD both for diagnostic purposes and for modification of treatment based upon measurable treatment outcomes. Systems, which do not directly measure [19-20, 22-23,26] cannot provide true AI. Through the use of the FMTVDM proprietary equations, QCA and FMTVDM can learn from each other without human intervention, marking the evolution to true AI.

**Figure 5:** Development of true artificial intelligence through machine learning removing human error from qualitative interpretation of results. The birth of true AI for diagnosing and treating coronary artery disease.

**Conflict of Interest**

FMTVDM patent issued to primary author. All figures reproduced by expressed consent of the primary author and remain his IP. There is no grant funding to report.

**Reference**


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