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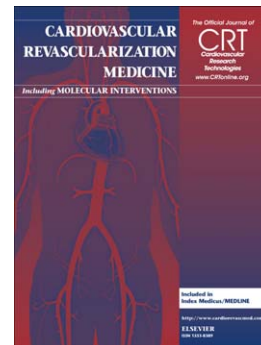
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# The effect of pre-procedure sublingual nitroglycerin on radial artery diameter and Allen's test outcome - relevance to transradial catheterization

Short running title: Sublingual NTG, radial artery diameter and Allen's test

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## Indexing words

Radial artery; radial spasm; angioplasty; nitroglycerin; Allen's test

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## Disclosures

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## Abstract

### Background:

The radial artery is increasingly used for cardiac procedures, but is a relatively small vessel that is prone to spasm when instrumented. Intra-arterial nitroglycerine has been shown to reduce radial spasm but first requires arterial access. We investigated the effect of pre-procedure sublingual nitroglycerin (NTG) on the diameter of the radial artery in a large cohort of patients.

### Methods:

305 subjects underwent ultrasound measurement of their radial and ulnar arteries in both arms before and after the administration of 800 micrograms of sublingual NTG. The Allen's test was also performed in the subjects prior to and after NTG.

### Results:

Radial artery diameter in this Caucasian study group is larger than that reported for other populations. The administration of sublingual NTG significantly increased the size of the right radial artery from  $2.88 \pm 0.36$  mm to  $3.36 \pm 0.40$  mm in men and from  $2.23 \pm 0.37$  up to  $2.74 \pm 0.36$  mm in women. There were also significant increases in left radial, right and left ulnar artery diameters in males and females with NTG. There was no significant effect of NTG on blood pressure. In all patients with an unfavourable Allen's test, retesting following sublingual NTG resulted in transition to a favourable Allen's.

### Conclusion:

Caucasian populations have larger calibre radial arteries compared to other geographic areas. Sublingual NTG is effective at dilating the radial artery in both men and women. This may make radial artery puncture and cannulation less challenging and should be considered in all patients in the absence of contraindications. The results of Allen's testing are dynamic and its usefulness for screening prior to transradial access is undetermined.

## Introduction

Adoption of the transradial access site for cardiac catheterization has gained considerable momentum in most countries, driven largely by a reduction in access site complications and mortality (in higher risk patients) combined with a clear patient preference when compared to the femoral approach(1–3). Radial procedures can be challenging, particularly in the early stages of the learning curve. One of the major problems encountered by operator is the difficulty in gaining access to and introducing equipment into the anatomically smaller radial artery compared to the larger femoral artery. Radial artery spasm can also complicate up to 15% of procedures(4), leading to anything from mild patient discomfort to severe spasm making catheter manipulation impossible(5). An unfavourable Allen test is also regarded as a contraindication to transradial access by some operators. Puncture failure, spasm and an unfavourable Allen test are the commonest reasons for switching to femoral access with all its attendant disadvantages.

Much of the work on reduction in radial spasm has revolved around administration of intra-arterial pharmacotherapy after radial access has been achieved. A recent meta-analysis by our group confirmed that intra-arterial verapamil, nitroglycerine and isosorbide mononitrate are all successful at reducing radial artery spasm(6). The intra-arterial administration of drugs does however first necessitate initial successful puncture and sheath insertion into the radial artery. This can be problematic as repeated attempts at gaining access of the radial artery itself are associated with spasm, hematoma formation and procedure failure(7). In SAFE-PCI for Women, access site crossover from transradial to transfemoral occurred more than 3 times as frequently in the presence of arterial spasm(8). The bare fingertip has a two point discrimination of 2 to 4 mm(9), which is likely to be worse when gloved. It is therefore unsurprising that first attempt radial puncture is not always successful. Some groups advocate the routine use of ultrasound guidance in aiding successful radial artery puncture, although this adds complexity to the procedure and carries a time penalty (5,10). Because of this routine use of imaging has not gained widespread acceptance. Patients with an unfavourable Allen test are assumed to have anatomically based fixed compromise in their hand collateral circulation, but little is known about reproducibility of Allen testing, in particular in relation to pharmacological manipulation.

Maximising the diameter of the radial artery increases the chances of first-attempt puncture success by palpation, especially during the early stages of an operator's learning curve. Nitroglycerin (NTG) releases the potent vasodilator nitric oxide in the presence of vascular smooth muscle(10). In this study, we investigated the effect of sublingual NTG on radial artery diameter in subjects with both favourable and unfavourable Allen's test.

## Methods

### Study population

The study population consisted of two groups of subjects: normal healthy individuals and

patients with coronary artery disease, diabetes mellitus, hypertension, chronic renal impairment not on dialysis. Healthy volunteers were recruited from staff at Royal Stoke University Hospital, a large tertiary cardiac centre that undertakes more than 2000 transradial PCI procedures annually, and patients from the cardiology outpatient department with the conditions specified above. The study was approved by the Local Ethics Committee and written informed consent was obtained from each participant. Subjects who were unable to give consent or who were acutely unwell were excluded.

#### Ultrasound study of forearm arteries

Two-dimensional vascular images and colour doppler ultrasonic studies of both the right and left forearm arteries were performed by an experienced cardiologist using a SonoSite TITAN portable ultrasound system (SonoSite Inc. Bothell, WA, USA) with a 10MHz linear vascular transducer. The transducer was placed perpendicular to the arterial wall to acquire an optimal image of the vessel. Once in position, the site was marked so that the same segment of the vessel was imaged throughout the study. The image was recorded in AVI format that transferred to an external computer for subsequent analysis.

The subjects lay supine in a temperature-controlled room with both arms comfortably abducted and the wrist supported. The luminal inner diameters of both the right and left radial artery (RA) and ulnar artery (UA) were measured immediately above the respective styloid processes in each arm. Measurement of the right RA and UA diameters was repeated after administering 800 µg of sublingual NTG. A second dose of 800 µg of sublingual NTG was administered after at least 30 minutes had elapsed to assess the effect of sublingual NTG on the left RA and UA diameters. The mean inner diameter was defined as an average value of 3 perpendicular readings.

#### Modified Allen's test

The modified Allen's test was performed by simultaneous compression of both the radial and ulnar arteries. The subject was then asked to make a fist and open their hand several times until the palm of the hand blanches. The compression on the UA was then released. The Allen's test is defined as favourable if full blushing of the hand occurs within 10 seconds. The test is unfavourable if it takes more than 10 seconds for full blushing to occur. For subjects with an unfavourable Allen's test, the test was repeated after sublingual NTG administration.

#### Data Collection

In addition to bilateral arterial diameters, subject characteristics, wrist circumference, hand dominance, Allen's test and blood pressure (BP) pre and post NTG were all recorded. Wrist circumference was measured two centimetres above the tip of the radial styloid process.

#### Reproducibility of measurements of forearm artery diameters

To assess reproducibility, the forearm diameters in 20 subjects were measured twice on

separate occasions at least two weeks apart.

### Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA). Categorical data were presented as absolute values and percentages whereas continuous data were presented as mean  $\pm$  standard deviation. The nature of distribution of the data was determined using 1-sample Kolmogorov-Smirnov test. Student's t test and Mann-Whitney U test were used to compare continuous data as appropriate. Categorical data were compared using the Chi-Square test with the appropriate degrees of freedom. Both univariate and multivariate regression analysis were used to examine potential correlation between radial artery diameter and variables such as sex, age, height, body mass index (BMI), hand dominance, hypertension, diabetes, chronic renal failure and peripheral vascular disease. A p value of less than 0.05 was considered to be statistically significant.

Intra-observer agreement was examined using intraclass correlation coefficient (ICC) and their 95% confidence intervals (CI).

## Results

### Subjects' characteristics

A total of 305 subjects were recruited, of which 125 were healthy volunteers. Baseline characteristics categorised by gender are detailed in Table 1. The male subjects were significantly taller and heavier and had a greater wrist circumference compared to the females. The Allen's test was unfavourable in a small proportion of subjects with a higher rate of unfavourable testing in females (table 1). The Allen's test was bilaterally unfavourable in a minority of subjects. After administration of NTG all unfavourable Allen's tests were augmented to become favourable.

### Diameters of forearm arteries and effect of NTG

The diameters (in mm) of the right (R) and left (L) radial and ulnar arteries pre- and post-NTG are listed in Table 2. Males had significantly larger wrist arteries than females ( $P < 0.0001$  for all comparisons). For both males and females, the radial artery at the wrist was bigger than the ipsilateral ulnar artery, and the right radial artery had the largest mean diameter. Sublingual NTG significantly increased the size of the RA and UA in males and females ( $P < 0.0001$  for all changes, see figures 1a and 1b). Nitrate administration was well tolerated and there was no significant difference in blood pressure measurements pre and post sublingual NTG.

### Radial artery diameters in relation to external diameters of arterial sheaths

Pre-sublingual NTG less than half of the female subjects had radial arteries capable of accommodating a standard 6F (external diameter 2.52mm) or 5F sheath (external diameter

2.28mm). Post-GTN there was a considerable improvement in the ability of the radial arteries to accommodate vascular sheaths. In males a similar pattern was present with nitrate mediated arterial dilatation improving the capacity to accommodate 5 and 6F sheaths (figure 2a and 2b).

#### Intraclass correlation coefficients

ICC for intra-observer agreement was excellent ranging from 0.95 for left UA measurement (CI 0.91 to 0.97) to 0.97 for right RA measurement (CI 0.94 to 0.98).

#### Logistic Regression analysis

Both univariate and multivariate regressions were used to examine the potential correlation between radial artery diameter and variables such as sex, age, height, body mass index (BMI), hand dominance, coronary artery disease, hypertension, diabetes, chronic renal failure and peripheral vascular disease. Gender was the only independent predictor of RA size (odds ratio 2.01, CI 1.427-2.353,  $P < 0.005$ ).

#### Discussion

The diameter of the RA plays an important role in the success of both arterial puncture and transradial cardiac procedures(11–13), especially during the early stage of an operator's learning curve. The mean RA diameter has previously been shown to be  $2.4 \pm 0.4$ mm in a Japanese population(11),  $2.6 \pm 0.4$ mm in a Korean population(13) and  $2.38 \pm 0.56$ mm in a Chinese population. Yan et al also measured the diameters of both left and right UA in a Chinese population, which were found to be of similar size to the RA(14).

To the best of our knowledge, our study is the first to examine forearm arterial diameters and the effect of sublingual NTG in a Caucasian (white with European ancestry) population using high resolution ultrasound. In this Caucasian population mean radial artery diameter is greater than that observed in other populations. Men have larger wrist arteries than women, and the RRA is the largest and hence easiest to puncture wrist artery in both genders. Importantly, fewer than 50% and 22% of women have a RRA diameter that is larger than the external diameter of a 5 French and a 6 French sheath respectively. This increases to more than 90% and 80% respectively with sublingual NTG. Although male arteries are larger, there is still a beneficial impact of nitrate on their ability to accommodate vascular sheaths. A study in an Indian population has previously shown that the injection of subcutaneous nitroglycerine significantly increases the diameter of the radial artery with consequent reduction in the number of attempted punctures(15), a finding consistent with our data. A French group has also shown that subcutaneous injection of NTG mixed with lignocaine is associated with quicker radial access in fewer attempts when compared to injection of lignocaine alone(16) further supporting the routine use of pre puncture nitrate for radial procedures. Our study confirms that administration of sublingual

NTG also results in a significant increase in the diameter of the radial artery, which is likely to increase the chance of successful radial puncture and cannulation. The increase in radial diameter will also reduce the risk of sheath induced overstretch which increases the chance of subsequent post procedure radial occlusion.

The use of sublingual NTG also has the added benefit of reducing arterial spasm, thus should make arterial cannulation and catheter manipulation easier. Although intra-arterial verapamil, nitroglycerine and isosorbide mononitrate have all been shown to reduce radial artery spasm(6), sublingual NTG has the advantage of administration prior to radial artery puncture and cannulation. Increasing the size of the radial artery prior to puncture and cannulation may also reduce the risk of radial artery occlusion following the procedure. There is data to suggest that the use of the RA for catheterisation can damage the intima and media(17), particularly in patients with smaller radial arteries(18) and lead to RA occlusion rates of up to 7%(19). Radial artery instrumentation can also lead to endothelial dysfunction due to denudation that can inhibit flow mediated dilatation(20). Radial artery trauma due to overstretch has been shown to be minimised by the use of smaller French sized catheters(18,19) with a key aspect being the ratio of RA diameter to external diameter of the sheath(21,22). Downsizing in sheath and catheter size and even sheathless procedures utilising balloon assisted tracking may help to reduce the size of the radial artery puncture(23). In more complex cases (for example during chronic total occlusion work) it is not always possible to reduce the size of the sheath or guiding catheters and increasing the size of the RA may help to reduce trauma.

Another novel observation with sublingual NTG was its effect on blood circulation to the hand. The Allen's test has been used to establish the presence of a collateral blood supply into the hand (usually from the ulnar artery). It has been shown that in the presence of an unfavourable Allen's test, 30 minutes of RA occlusion leads to reduced blood flow to the thumb and an increase in thumb capillary lactate(24), leading in the past, to a call for an unfavourable Allen's test to be a contraindication to RA procedures. In our study, all patients who were found to have an unfavourable Allen's test at the start of the study had their Allen's test repeated after administration of sublingual NTG. The test always became favourable, indicating a dynamic circulation that is recruitable, providing a plausible explanation to why radial artery occlusion is usually asymptomatic. In our study we used only the modified Allen's test and not the Barbeau test (which uses pulse oximetry and assesses the waveform during occlusion of the radial artery). Use of the Barbeau test may have given us further information on the effect of NTG on the radial artery. Our results are consistent with more recent work which has shown that across a range of Allen's test results (normal, intermediate and abnormal), there was no difference in measured thumb capillary lactate following transradial angiography(25).

Our study does have limitations. All subjects were from a single centre in the United Kingdom and all measurements performed by a single operator (TL). Although we have demonstrated that sublingual NTG has a significant impact on the diameter of the radial



artery, we have not proven that this results in any clinical benefit such as reducing the number of attempts to radial puncture, increasing the likelihood of a successful procedure or reducing the rates of radial artery occlusion. Finally, we do not have information on medications that patients included in the study were taking at the time of the examination of their radial and ulnar arteries. It is possible that some patients were on oral medications (for example, long acting nitrates) that may have influenced the effect of sublingual NTG.

### Conclusion

In a Caucasian population, the RA is significantly smaller in women than men, with the majority of RA in women smaller than the external diameter of a 5 French sheath prior to sublingual NTG. The RA is larger than the UA and the RRA larger than the LRA in most men and women. Sublingual NTG increases the size of the RA significantly and should facilitate RA puncture, potentially shortening the learning curve associated with the transradial technique. The effect of sublingual NTG on unfavourable Allen's test illustrates the dynamic properties of the forearm circulation and questions the usefulness of testing prior to transradial catheterization. Administration of sublingual NTG is safe, and in the absence of contraindications, our data suggests that it should be standard practice prior to transradial catheterization.

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**Table 1.** Study subject characteristics grouped according to gender

	Male (n=150)	Female (n=155)	P value
Age	60.1±16.7	57.3±16.9	0.145
Height (m)	1.77±0.08	1.65±0.06	<0.0005
Weight (kg)	83.6±13.7	72.4±17.1	<0.0005
BMI	26.7±4.5	26.7±5.9	0.024
R wrist circumference (cm)	18.8±1.5	17.0±1.6	<0.0001
L wrist circumference (cm)	18.4±1.7	16.8±1.6	<0.0001
Negative R Allen's test (%)	6 (4%)	7 (4.5%)	N/A
Negative L Allen's test (%)	4 (2.7%)	8 (5%)	N/A
Bilateral Negative Allen's test (%)	1 (0.7%)	1 (0.6%)	N/A
Smoker (%)	57 (32%)	46 (30%)	0.64
Hypertension (%)	38 (25%)	44 (28%)	0.75
Diabetes (%)	31 (20.7%)	29 (18.7%)	0.82
Coronary artery disease (%)	45 (30%)	42 (27%)	0.56
Peripheral vascular disease (%)	8 (5.3%)	10(6.5%)	0.87
Chronic renal failure (%)	10(6.7%)	10(6.5)	0.92

**Table 2.** Diameters of wrist arteries and blood pressure pre and post NTG grouped according to gender

	Male (n=150)	Female (n=155)	Mean diameter difference	P value
<b>Pre NTG</b>				
RRA (mm)	2.88±0.36	2.23±0.37	0.65	<0.0001
LRA (mm)	2.63±0.38	2.14±0.35	0.49	<0.0001
RUA (mm)	2.57±0.36	2.16±0.38	0.41	<0.0001
LUA (mm)	2.46±0.49	2.09±0.35	0.37	<0.0001
<b>Post NTG</b>				
RRA (mm)	3.36±0.40	2.74±0.36	0.62	<0.0001
LRA (mm)	3.11±0.41	2.59±0.40	0.52	<0.0001
RUA (mm)	3.08±0.37	2.61±0.35	0.47	<0.0001
LUA (mm)	2.92±0.47	2.51±, 0.36	0.41	<0.0001
<b>Blood Pressure (mmHg)</b>				
Pre NTG	116/72±18/12	113/70±15/10	3/2	NS
Post NTG	110/68±16/9	106/65±12/9	4/3	NS

## Figure Legend

**Figure 1a.** Mean diameters (mm) and percentage change of right radial artery, left radial artery, right ulnar artery and left ulnar arteries pre and post sublingual NTG in men ( $p < 0.0001$  for all changes in diameter).

**Figure 1b.** Mean diameters (mm) and percentage change of right radial artery, left radial artery, right ulnar artery and left ulnar arteries pre and post sublingual NTG in women ( $p < 0.0001$  for all changes).

**Figure 2a.** Percentage of men with RRA and LRA diameters  $> 2.28\text{mm}$  and  $> 2.52\text{mm}$ , respective external diameters of standard 5F and 6F arterial sheaths.

**Figure 2b.** Percentage of women with RRA and LRA diameters  $> 2.28\text{mm}$  and  $> 2.52\text{mm}$ , respective external diameters of standard 5F and 6F arterial sheaths.

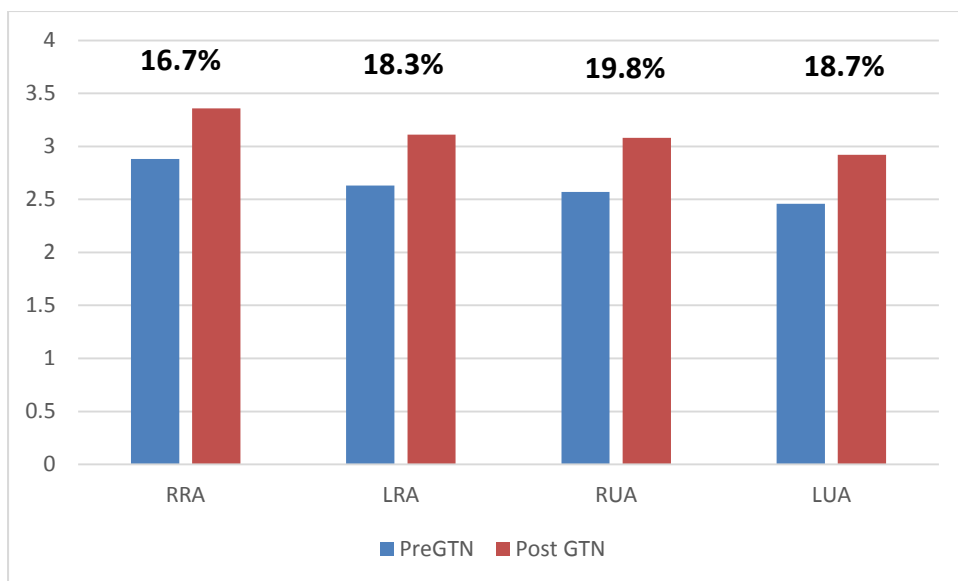


Figure 1a



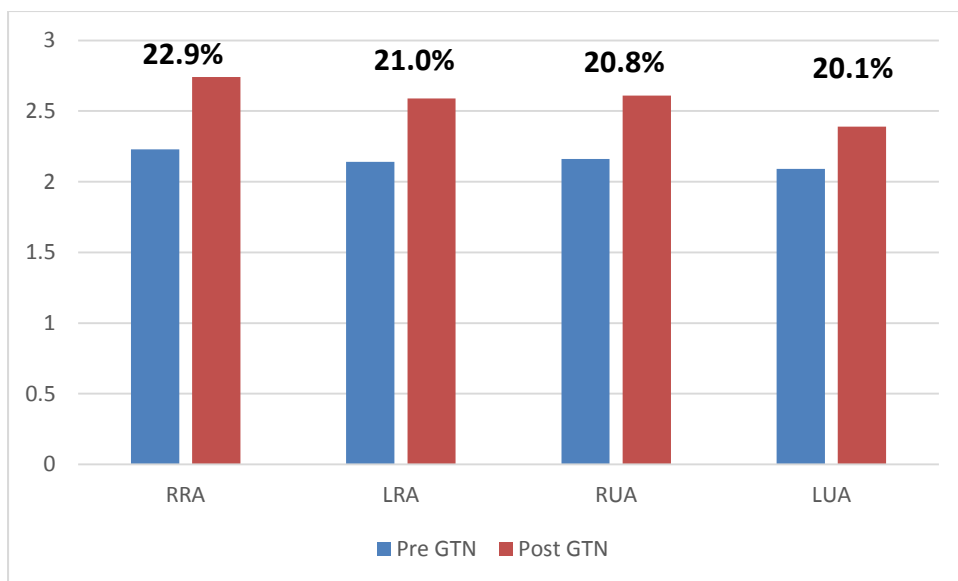


Figure 1b

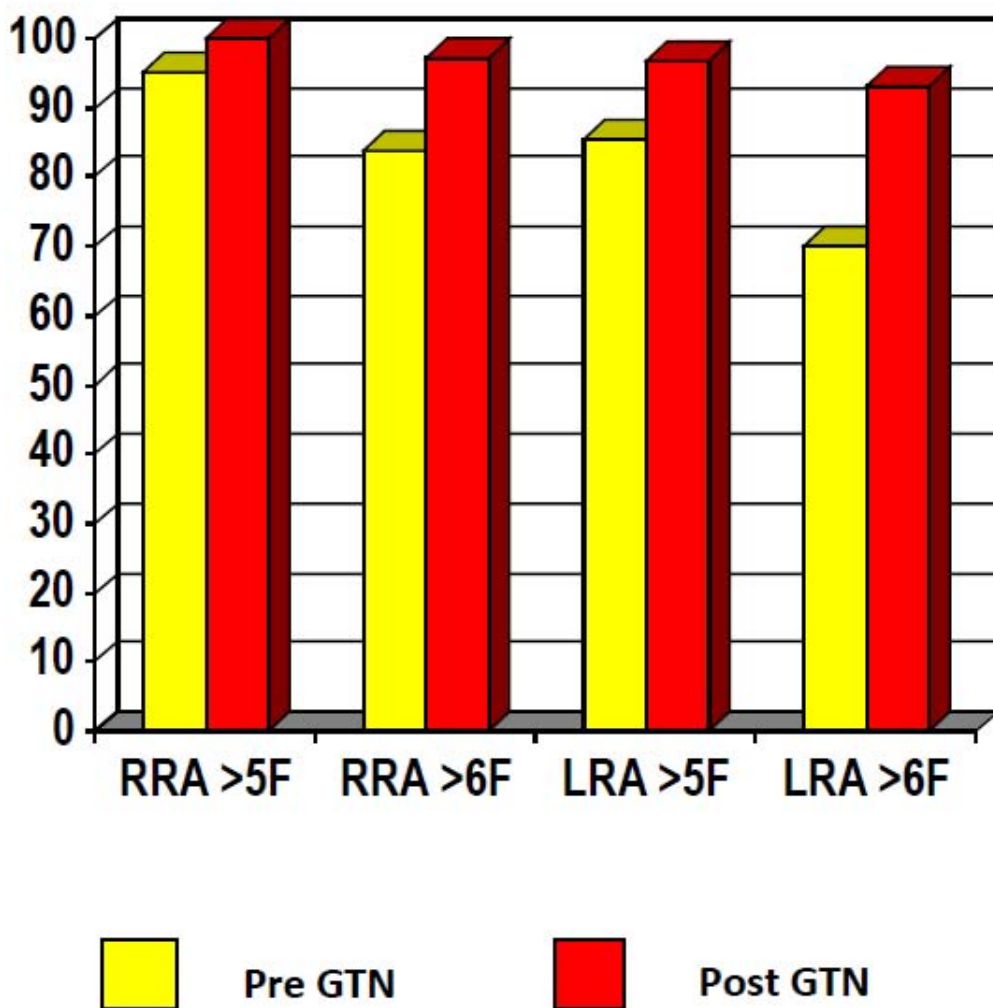


Figure 2a

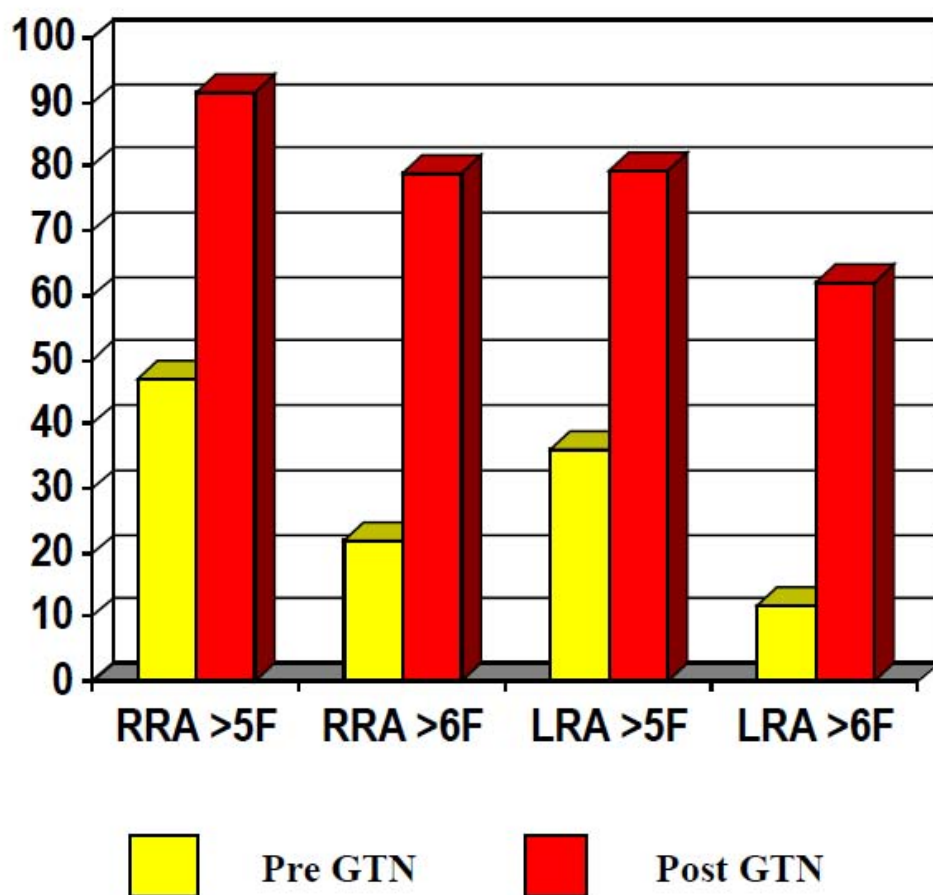


Figure 2b

**Highlights**

-The radial artery is a small vessel that is increasingly used for coronary angiography and angioplasty

-The use of pre-procedural sublingual nitroglycerin (NTG) significantly increases the size of the radial artery in men and women

-The use of pre-procedural NTG renders an initially unfavourable Allen's test positive

-The use of sublingual NTG should be considered in all patients undergoing transradial coronary procedures