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Comparison of Coronary Vasodilation and Systemic Hemodynamic Effect of Two Doses of Intracoronary Sodium Nitroprusside for Coronary Fractional Flow Reserve

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Abstract

Background: Intracoronary bolus of 100 mcg of sodium nitroprusside (IC-NTP) produces the same FFR response as intravenous infusion of adenosine (IVA). However; it causes significant decrease in systemic arterial blood pressure. The purpose of this study was to compare FFR response and systemic hemodynamic effects of low dose (50μg) with high dose (100μg) of IC-NTP.

Methods: We prospectively studied 36 coronary stenosis in 18 patients. FFR, Blood Pressure (BP) and Heart Rate (HR) were measured after intracoronary boluses of 50 and 100mcg of NTP and IVA (140μg/kg/min). IC-NTP boluses were given over <3 seconds. IVA was infused for 150 seconds. Repeated FFR measurements were performed only after resting coronary gradient (Pd/Pa) ratio, BP and HR returned to baseline.

Results: There was no significant difference in FFR values obtained after 50μg IC NTP, 100μg IC NTP and IVA (0.805±0.115, 0.804±0.113, 0.807±0.100, respectively, F=1.2, p=0.32). Correlation of FFR values obtained after lower and higher dose of NTP was excellent (r= 0.97, p<0.001). Decrease in blood pressure was significantly lower after 50μg IC NTP as compared to 100μg of IC NTP (systolic BP: 4.2% *vs*. 12%, t=4.3, p<0.001, diastolic BP: 3.6% *vs*. 7%, t=2.1, p=0.04, mean BP: 2% *vs*. 8%, t=3.7, p<0.001). No patients reported any side effects after IC NTP.

Conclusion: Intracoronary bolus of 50mcg IC-NTP results in similar coronary hyperemia as 100mcg and or IVA. Lower dose of IC NTP results in significantly less systemic hypotension and should be preferred dose in subjects with contraindications to adenosine or borderline blood pressure.

Keywords: Adenosine; Coronary artery disease; Fractional flow reserve; Hyperemia; Sodium nitroprusside

Summary

Intracoronary sodium nitroprusside at a dose of 50 micrograms evokes FFR response comparable to FFR induced by 100 micrograms of sodium nitroprusside and intravenous infusion of adenosine (140μg/kg/min for 150 seconds). As opposed to intravenous adenosine and 100μg of sodium nitroprusside, intracoronary sodium nitroprusside at a dose of 50μg has minimal effects on systemic blood pressure.

Introduction

Fractional Flow Reserve (FFR) measurement is now routinely used to assess hemodynamic significance of intermediate coronary artery stenosis and guide percutaneous coronary intervention [1,2]. Its diagnostic accuracy heavily relies on the ability to achieve maximal coronary hyperemia, as submaximal coronary vasodilation leads to underestimation of the functional severity of stenosis [3-5]. Intravenous adenosine is currently the most commonly used pharmacologic agent for FFR study [6,7]. However, it is expensive, requires cumbersome and time demanding setup and not well tolerated or contraindicated in patients with reactive airway disease, advanced cardiac conduction disorders or concomitant therapy with dipyridamole [8-10]. Intracoronary adenosine has a lower rate of systemic effects than intravenous infusion, but it appears that previously recommended doses do not evoke maximal coronary hyperemia and currently there is no agreement which dose should be used as a "standard" [11-13]. Sodium nitroprusside (NTP) appears to be a very reliable, convenient and inexpensive alternative to adenosine [14-17]. We have shown that intracoronary bolus of NTP at a dose of 100μg has better sensitivity than intravenous adenosine (140μg/kg/min) and is better tolerated by patients [14]. However, intracoronary bolus of NTP at the dose of 100μg, leads to transient, although significant decrease in systemic blood pressure, which can be potentially harmful in patients with severe LV dysfunction or low systemic blood pressure. The aim of this study was to assess whether lower dose of intracoronary NTP will have less systemic hemodynamic effect and at the same time retains maximal coronary vasodilatory

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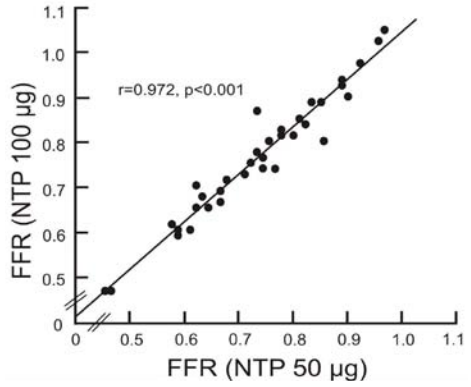

Figure 1: Correlation of FFR values obtained after 50µg and 100µg of intracoronary bolus of sodium nitroprusside. FFR = Fractional Flow Reserve, NTP = Sodium Nitroprusside.

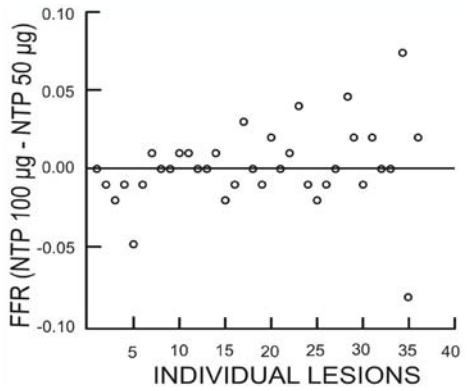

Figure 2: Individual differences between FFR induced by 50µg and 100µg of intracoronary sodium nitroprusside. FFR = Fractional Flow Reserve, NTP = Sodium Nitroprusside.

effects. We compared FFR response and effects on systemic blood pressure of 100µg and 50µg NTP given as an intracoronary bolus.

Materials and Methods

Study population

We routinely use both IV adenosine and IC NTP (100mcg bolus) to assess FFR response as De Luca et. al. demonstrated lack of full hyperemia with a high percentage of subjects treated with IV adenosine. If FFR values obtained with IC NTP and IV adenosine are discrepant we consider the lower value to make a decision regarding coronary intervention. We used the lower value when discrepant results were obtained as it has previously been shown that patients can be non-responders to adenosine, and have also been noted to not achieve maximal hyperemia despite higher doses of nitroprusside or adenosine. We studied 36 coronary artery stenotic lesions in 18 consecutive patients who underwent clinically indicated FFR at the University Hospital between July 2012 and October 2012. The study was approved by the University Hospital Institutional Review Board.

Coronary angiography

A standard percutaneous femoral approach was used to obtain arterial access. Diagnostic coronary angiography was performed by the Judkins technique with 6-F right and left coronary catheters. The electrocardiogram, arterial blood pressure and arterial oxygen saturation were continuously monitored throughout the procedure. Decision to perform FFR measurements was based on visual assessment of the stenotic lesion.

Pressure measurements

After administration of intravenous heparin (60U/kg), a guiding catheter was inserted. Guiding catheters without side holes were used. Intracoronary nitroglycerine 150µg bolus was injected via the guiding catheter. A 0.014-inch high-fidelity pressure-recording guide wire (Prime Wire, Volcano, San Diego, California) was externally calibrated (zeroed) and then the wire was advanced to the tip of the guiding catheter. It was verified that the measured pressures in the pressure wire and the guiding catheter were equal (normalization). Subsequently, the pressure wire was advanced into the coronary artery with the pressure sensor placed distal to the target lesion site. Distal coronary and aortic pressures were measured at baseline and at maximal hyperemia. Pressure signals were continuously recorded at a baseline speed of 25mm/s, and a beat-to-beat analysis of mean pressure was performed. Once stable pressure signal was obtained, measurements were recorded. FFR was calculated as a ratio of intracoronary pressure (Pd) to aortic pressure (Pa) obtained during maximal hyperemia. FFR < 0.8 was considered hemodynamically significant [2].

Pharmacological protocol

Once pressure wire sensor was positioned distal to the interrogated lesion, NTP at a dose of 50µg (0.5mL of 20mg in 250mL D5W) was injected over 3 seconds via the guiding catheter. After injection Pd/ Pa ratio, blood pressure and heart rate were monitored until all parameters returned to baseline levels. Subsequently bolus of IC NTP at the dose of 100µg (1mL of 20mg in 250mL D5W) was given. The time to reach maximal hyperemia and the duration of steady-state maximal hyperemia after each NTP injection was recorded. After Pd/ Pa ratio, blood pressure and heart rate returned to baseline level, a peripheral IV infusion of adenosine at a dose of 140µg/kg/min was administered through a major arm vein with the use of rate-controlled infusion pump. Infusion was continued for a minimum of 150 seconds and FFR was measured when steady-state hyperemia was achieved. Nitroprusside was given first as to avoid the potential incremental effects of adenosine before the use of nitroprusside.

Statistical analysis

All analyses were performed using STATISTICA® for Windows version 8 (Stat Soft Inc., Tulsa, Oklahoma). Normality of distribution of continuous variables was checked with Kolmogorov-Smirnov test. Data are presented as mean ± SD. Continuous variables were compared using paired t-test. Multiple comparisons were performed with repeated measures ANOVA. If statistical significance was found, post hoc Bonferroni test was used. Correlations were calculated using Pearson's correlation coefficient. A p value of < 0.05 was considered significant. A formal power calculation was not performed at the time of the study initiation as the investigation is a pilot study by design.

Results

Baseline characteristics: We consecutively studied 18 patients (15 males and 3 females) of mean age 63±6 years and weight of 86±21kg. Mean baseline heart rate (HR) was 72±11 beats/min. Systolic, diastolic

and mean arterial pressures were: 144±30, 78±12 and 101±15 mmHg, respectively. All patients were in sinus rhythm at the beginning of the procedure. Indications for coronary angiography were: positive stress test in 9 patients, unstable angina in 4 patients and Non ST-Elevation Myocardial Infarction (NSTEMI) in 4 patients. Baseline angiographic characteristics are reported in Table 1.

Comparison of FFR induced by two doses of intracoronary sodium nitroprusside and intravenous adenosine: There was no statistically significant difference in mean FFR values obtained after 50μg IC NTP, 100μg IC NTP and IV adenosine (0.805±0.115, 0.804±0.113, 0.807±0.100, respectively, F=1.2, p=0.32). We found excellent correlation of FFR values obtained after 50μg IC NTP and 100μg IC NTP (Pearson's correlation coefficient: r= 0.97, p<0.001) (Figure 1). The mean difference between FFR induced by "low" and "high" dose of IC NTP was 0.015±0.017. The maximum individual difference was 0.08 (Figure 2). There were no instances where the difference in FFR obtained after "low" and "high" dose of IC NTP led to reclassification of the lesion (significant *vs.* non significant). There was no association between weight of the patient and FFR response to intracoronary nitroprusside (for 50μg NTP: R2 = 0.02, F=0.1, p=0.75, Pearson's correlation coefficient: r= 0.05). Time to maximal decrease in FFR after both "low" and "high" dose IC NTP injections was always between 5 and 10 seconds. Duration of hyperemia after "low" and "high" doses of IC NTP ranged between 30 and 60 seconds and was not significantly different between the 2 doses. This is an observation that has been previously seen with nitroprusside, as well throughout the medical literature, that the pharmacokinetics do not seem to be identical to the pharmacodynamics.

Effects of "low" and "high" dose of intracoronary sodium nitroprusside and intravenous adenosine on hemodynamic parameters: IC NTP at the dose of 100μg significantly reduced systolic blood pressure (144±30 *vs.* 127±22 mmHg, p<0.001), diastolic blood pressure (78±12 *vs.* 73±14 mmHg, p=0.03) and mean blood pressure (101±15 *vs.* 93±15, p=0.01) (Figure 3). Lower dose of IC NTP significantly reduced systolic blood pressure (144±30 *vs.* 138±27 mmHg, p=0.03), and had no effect on diastolic blood pressure (78±12 *vs.* 76±12 mmHg, p=0.33) and mean blood pressure (101±15 *vs.* 99±15, p=0.44) (Figure 3). Decrease in systemic blood pressure was significantly lower after 100μg IC NTP as compared to 50μg of IC NTP (systolic blood pressure: 12% *vs.* 4.2% decrease, t=4.3, p<0.001, diastolic blood pressure: 7% *vs.* 3.6% decrease, t=2.1, p=0.04, mean blood pressure: 8% *vs.* 2% decrease, t=3.7, p<0.001). There was no association between weight of the patient and blood pressure response after intracoronary nitroprusside (for 50μg NTP: R2 = 0.02, F=0.69, p=0.41, Pearson's correlation coefficient: r= 0.15). Intravenous adenosine significantly reduced systolic blood pressure (144±30 *vs.* 129±29 mmHg, 11% decrease, t=2.8, p=0.01), diastolic blood pressure (78±12 *vs.* 71±14 mmHg, 9% decrease, t=2.5, p=0.02) and mean blood pressure (101±15 *vs.* 93±18 mmHg, 8% decrease, t=2.2, p=0.04) (Figure 3). Baseline heart rate (72±11 beats/minute) was not significantly affected by low dose IC NTP (75±15 beats/minute), high dose IC NTP (76±14 beats/minute) and IV adenosine (77±15 beats/minute), F=2.66, p=0.06.

Table 1: Baseline angiographic characteristics. Reported values are total numbers, values in brackets are percentages of a total number. FFR – Fractional Flow Reserve, LAD – Left Anterior Descending Artery, DIAG – Diagonal Branch, LCX – Left Circumflex Artery, RCA – Right Coronary Artery.

Number of vessel interrogated in a single patient	
Total number of patients	18
Single vessel interrogated	8 (44%)
Two or more vessels interrogated	10 (56%)
Target vessel for FFR	
Total number of stenotic lesions	36
LAD	7 (20%)
DIAG	9 (25%)
LCX	17 (47%)
RCA	3 (8%)
Lesion location	
Total number of stenotic lesions	36
Ostial	2 (6%)
Proximal	7 (19%)
Mid	17 (47%)
Distal	10 (28%)

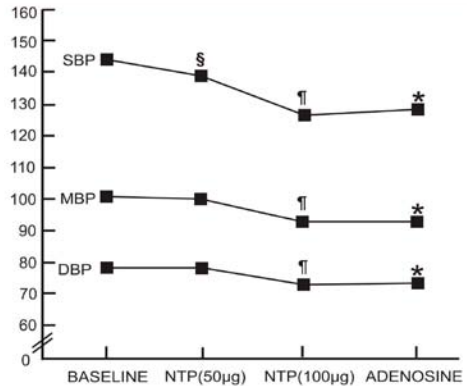

Figure 3: Effect of two doses of intracoronary sodium nitroprusside and intravenous adenosine on systemic arterial blood pressure. *, ¶, § - significant differences versus baseline blood pressure. SBP = Systolic Blood Pressure, MBP= Mean Blood Pressure, DBP = Diastolic Blood Pressure, NTP = Sodium Nitroprusside.

Side effects profile: During adenosine infusion 9 patients (50%) reported at least one side effect. Eight patients (50%) reported headache and 5 patients (27%) reported dizziness and flushing. No patients reported unpleasant symptoms after NTP injection. Blood pressure returned to baseline within 60 seconds after injection of NTP or discontinuation of intravenous adenosine infusion.

Discussion

This study demonstrates that intracoronary bolus of 50μg NTP produces the same FFR response as NTP at the dose of 100μg. As opposed to 100μg NTP, lower dose has minimal effect on systemic blood pressure. Both doses of NTP are much better tolerated than intravenous adenosine.

We have chosen to study 50μg dose based on former studies [13-17] which suggested that intracoronary NTP at doses of 0.6μg/kg evoked similar coronary hyperemia with less hypotensive effects than 0.9μg/kg dose. Since the mean weight of our population was

85kg, the 50μg dose translates to weight based NTP dose 0.58μg/kg. Excluding one morbidly obese patient the weight range of our study population was relatively narrow (50 -93 kg); hence the highest and lowest administered doses were 1μg/kg and 0.53μg/kg, respectively. As we found very poor correlation between patient weight and FFR or systemic blood pressure response we do believe that the dose/response curve for intracoronary NTP is much flatter than for systemically administered NTP suggesting that the administration of fixed dose NTP did not affect the results of our study.

Low dose of NTP evokes the same FFR response as a higher dose NTP and intravenous adenosine. This is in congruence with most other studies [15-17] and in contradiction with the NASCI [13] study which found that 0.6μg/kg dose of intracoronary NTP was significantly less effective than intravenous adenosine. We are not able to explain this discrepancy, however it should be pointed that in NASCI study NTP was administered as a fourth agent, after three large doses of adenosine. It is known that vasodilatory effects of adenosine are at least partly mediated by nitric oxide production [18,19]. We can hypothesize that overstimulation with adenosine may partially exhaust nitric oxide dependent vasodilatory mechanism on different levels including second messenger pathway as well as KCa channels.

We found that 50μg dose of NTP has minimal effects on systemic blood pressure. Although decrease in systolic blood pressure was still significant as compared to baseline values, 4.2% decrease does not seem to have any clinical significance even in patients with borderline blood pressure. Parham et-al. noted more excessive systolic blood pressure nadir even with the dose of 0.3μg/kg (15%) [15]. Our results are similar to results of Leone et all who found about 5% decrease in systolic blood pressure after administration NTP at the dose of 0.6μg/kg [13]. Li reported a drop in systolic and diastolic pressure (16 and 12 mm Hg respectively) after a bolus of 0.6μg/kg. In our study the lower dose of nitroprusside was administered as a first agent (before higher dose of NTP and IV adenosine) to make sure FFR and systemic effects were assessed on "vasodilator naive" patients.

In this study intravenous adenosine had heterogeneous hypotensive effect that was quite pronounced in 3 patients (while evaluating 5 coronary stenoses) and on average was comparable to the hypotensive effects of 100μg of NTP. Li [16] noted hypotensive response to IV adenosine (Average drop of 14 and 11 mm Hg in systolic and diastolic blood pressure respectively) were similar to a 0.6μg/kg NTP (average systolic and diastolic blood pressure reduction of 14 and 11 mmHg respectively) . It is intriguing that multiple studies report inconsistent results regarding effects of intravenous adenosine on systemic blood pressure [6,13,14,20]. Clearly, not well defined clinical covariates affect propensity to hypotensive response to adenosine.

Consistent with results of our previous study and others [16] adenosine caused unpleasant side effects in >50% of our patients. Although none of these effects led to cessation of the infusion, it caused significant discomfort of patients during the procedure. Sodium nitroprusside was very well tolerated and no unpleasant symptoms were noted by any of the patients.

Study limitations: We recognize that this is relatively small study and therefore it has a low power and is susceptible to outlier effect. However, the range difference between the FFR of the 2 doses tested was relatively narrow and it is very unlikely that larger study would be able to generate significant difference in FFR between low and high dose of NTP. Likewise, despite small study population we were able to find significant differences in blood pressure response to low and high dose of NTP. Blood pressure response to both doses of NTP was relatively constant and we did not find significant outlier values.

Conclusions

This study shows that intracoronary sodium nitroprusside at a dose of 50μg is as effective as 100μg dose and intravenous adenosine for assessment of hemodynamic significance of coronary artery stenosis without having significant effects on systemic blood pressure.

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