Prognostic value of Angiographic Perfusion Score (APS) following percutaneous interventions in acute coronary syndromes

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Introduction: Identifying reperfusion and predicting post procedure risk is important following Percutaneous Coronary Interventions (PCI). An Angiographic Perfusion Score (APS) combining TIMI flow (TFG) and myocardial perfusion (TMPG) grades before and after PCI can accurately measure both epicardial and myocardial perfusion and predict Major Adverse Cardiac Events (MACE).

Patients and methods: APS was calculated in 226 (88 ST elevation Myocardial Infarction (STEMI) and 138 Non STEMI) patients. Maximum score being 12, reperfusion was defined as failed: 0–3, partial: 4–9, and full APS: 10–12. Thirty day MACE were observed.

Results: APS identified reperfusion significantly more than TMPG alone (STEMI: 50.6% vs 11.8% (p<0.001); Non STEMI, early reperfusion: 69.4% vs 52.8% (p<0.01) and Non STEMI late reperfusion: 38.2% vs 7.8%; (p<0.001) respectively. A significantly lower incidence of MACE was observed in the full as compared to the failed APS group (1.8% vs 22.5%) (p<0.001). No differences were noted between TMPG 0–2 (9.8%, 9.4%, 7.3%, respectively) (p=NS).

Conclusion: Compared to MPG alone APS detects more low risk reperfused patients, post PCI.

1. Introduction

Reperfusion therapy in acute myocardial infarction (AMI) aims at early and sustained reperfusion of the myocardium at risk. Reperfusion therapy is considered to be angiographically successful when a good TIMI (thrombolysis in myocardial infarction) flow is achieved in the infarct-related coronary artery.1–3 Improved epicardial flow assessed by TIMI flow grades (TFG) has been related to reduced mortality after coronary revascularization.1–5 However, even when a good TIMI flow is achieved, some patients have less than optimal reperfusion at the tissue level, and myocardial reperfusion is...
not always achieved in patients with a successful percuta-
neous coronary intervention (PCI). Several mechanisms have
been suggested to be involved such as no reflow and distal
embolization.5–7

TIMI myocardial perfusion grade (TMPG) is an angiographic
measure of myocardial perfusion at capillary level.4 TMPG has
been found to be useful in both pharmacological and catheter
based reperfusion after AMI and is suggested as a useful
indicator of successful myocardial reperfusion.5 Patients with
both normal epicardial flow and myocardial perfusion have
been shown to have a very low mortality rate of 0.73%.8 Thus,
the TMPG adds additional prognostic information to the
conventional epicardial TFG.9 Incorporation of these two
variables envisaging a combined index of epicardial and
myocardial microvascular blood flow has been suggested as
the Angiographic Perfusion Score (APS).10 APS is a simple,
angiographic metric that takes into account indices of
epicardial and myocardial perfusion, both before and after
PCI, to arrive at a single perfusion grade. The APS is the sum
of the TFG (0–3) added to the TMPG (0–3) before and after PCI,
therefore, a total grade of 0–12 is possible. Failed perfusion
was defined as an APS of 0–3, partial perfusion as an APS of
4–9, and full perfusion as an APS of 10–12. Among STEMI
patients with larger infarct sizes, the association of APS with
the incidence of death or MI, has been found to be statistically
significant with none dying on an APS score of 10–12 and
mortality being higher among patients with a poorer APS
score (0–9) (p = 0.03).10

Evidence thus favors that the APS, which combines grades
of epicardial and tissue level perfusion before and after PCI
may be closely associated with infarct size, and may prove
valuable in clinical risk stratification. Limited prospective
data is available on the use of APS for risk stratification,
especially when compared to the conventional TMPG and
more so in the Non ST elevation MI/unstable angina
(NSTEMI/UA) patient group undergoing PCI. The aim of this
study was to compare assessment of reperfusion post PCI in
acute coronary syndrome (ACS) using the standard TMPG
which takes into consideration post procedure myocardial
perfusion alone, as compared to a more comprehensive
assessment with APS that combines TIMI flow and TMPG
before and after PCI, thereby reflecting both epicardial
and myocardial flow, and to see if APS is a better reflector
of reperfusion as well as favorable short term risk versus
TMPG.

2. Methods

Consecutive patients presenting with ACS undergoing PCI
were included in the study. All eligible patients were evalu-
ated with detailed history and thorough clinical evaluation.
Biochemical and hematological parameters including hemo-
globin, total and differential leukocyte count, platelet count,
blood sugar, lipid profile, blood urea, serum creatinine,
sodium potassium were noted along with baseline CK–MB and
Troponin T. Baseline ECG and Echocardiography were
performed. Procedural coronary angiograms were evaluated by
two consultants independently; TFG, TMPG, and APS were
calculated before as well as after PCI.

2.1. Definitions

The following definitions were used

1) TFG for epicardial flow assessment

- **TFG 0**: No perfusion; no antegrade flow beyond the point of
  occlusion,
- **TFG 1**: Penetration without perfusion; the contrast material
  passed beyond the area of obstruction but "hanged up" and
  failed to opacify the entire coronary bed distal to the
  obstruction for the duration of the cine run.
- **TFG 2**: Partial perfusion; the contrast material passed
  across the obstruction and opacified the coronary bed distal to
  the obstruction, the rate of entry of contrast into the vessel
distal to the obstruction and/or its rate of clearance from the
distal bed being perceptibly slower than its entry into and/or
  clearance from comparable areas not perfused by the culprit
  vessel and,
- **TFG 3**: Complete perfusion with antegrade flow into the
  bed distal to the obstruction occurs as promptly as into the
  bed proximal to the obstruction and clearance of contrast
  material from the involved bed is as rapid as from an uninvol-
  vured bed in the same vessel or the opposite artery.

2) TIMI Myocardial Perfusion Grade (TMPG) for myocardial
perfusion,

- **TMPG 0**: Dye failed to enter the microvasculature; either
  minimal or no ground glass appearance ("blush") or opacifi-
  cation of the myocardium in the distribution of the culprit
  artery indicating lack of tissue level perfusion.
- **TMPG 1**: Dye slowly entered but failed to exit the micro-
  vasculature; ground glass appearance ("blush") or opacifi-
  cation of the myocardium in the distribution of the culprit
  lesion that failed to clear from the microvasculature; dye staining
  present on the next injection (approximately, 30 seconds
  between injections).
- **TMPG 2**: Delayed entry and exit of dye from the micro-
  vasculature; ground glass appearance ("blush") or opacifi-
  cation of the myocardium in the distribution of the culprit
  lesion strongly persistent at the end of the washout phase (i.e.,
  strongly persistent after 3 cardiac cycles of the washout
  phase; either none or minimal diminution in intensity during
  washout) and,
- **TMPG 3**: Normal entry and exit of dye from the microvas-
  culature; ground glass appearance ("blush") or opacification
  of the myocardium in the distribution of the culprit lesion
  that cleared normally; either gone or only mild/noticeable
  diminution in intensity during the washout phase), similar to that
  in an uninvolved artery to allow blush grading, the length of the
  angiographic run was allowed long enough till the venous
  phase of the contrast passage was seen. Blush was assessed
distal to the culprit lesion, and views were chosen to minimize
superimposition of noninfarcted territories in the assessment
of the TMPG for the culprit artery. Care was taken not to
mistake filling of the venous system, such as the great cardiac
vein, as blush. Blush was assessed during the same phase of
the cardiac cycle, since it tends to be less intense during the
diastole. These angiographic runs were made in identical
views according to the infarct-related artery thus assuring assessment in equal conditions. When the left coronary artery was involved, the final angiogram was made in the left lateral view. When the right coronary artery was involved, the final angiogram was made in the right oblique view. During contrast injection, backflow of the contrast agent into the aorta had to be present in order to be certain of adequate contrast filling of the epicardial coronary artery. All angiograms were made with 6F or 7F guiding catheters following the standard procedure. An intracoronary bolus of 200 μg nitroglycerin was given immediately after the angioplasty procedure to allow adequate quantitative coronary artery analysis.

3) Angiographic Perfusion Score (APS) was then derived by calculating the sum of the TIMI flow grade (TFG; 0–3) added to the TIMI myocardial perfusion grade (TMPG; 0–3) before and after PCI (total possible grade, 0–12). Failed perfusion was defined as an APS of 0–3, partial perfusion as APS of 4–9, and full perfusion as a full APS of 10–12.

Post PCI, CK- MB levels, serum creatinine and platelet counts were obtained 24 h after the procedure. Major Adverse Coronary Events (MACE) were defined as a composite of death, reinfarction or ischemic-driven target vessel revascularization. Reinfarction was defined as elevation of CK- MB enzyme levels three times above its upper limit of normal associated with ischemic symptoms. Follow up was done in patients coming to the hospital on routine basis after 30 days of procedure or earlier because of symptoms. A routine echocardiographic examination was done in all patients attending the PCI clinic to determine the left ventricular ejection fraction (LVEF).

### 2.2. Statistical analysis

All analyses were performed with SPSS version 15 software. All continuous variable values are reported as the mean plus or minus standard deviation or the median and interquartile range. The student t test was used for the analysis of continuous variables. When appropriate, the χ² test or Fisher exact test were used for the analysis of categorical variables.

### 3. Results

A total of 226 patients, 88 (39%) with STEMI and 138 (61%) with NSTEMI who underwent PCI were evaluated for reperfusion using the APS and TMPG and their relation with 30 day MACE. None of our patients received Abciximab or any other GP IIb/ IIIa inhibitor pre PCI. Two boluses of intracoronary integrilin was given in those with visible thrombus where thrombectomy was done. Adenosine was given in routine doses in case of slow or no reflow situations.

#### 3.1. STEMI (Table 1)

Of the 88 patients presenting with STEMI, primary PCI was performed in 3 and rescue/routine PCI was undertaken in the rest. All patient not getting primary PCI received thrombolysis with Streptokinase. 1.5 million units infusion over 1 hour. Thrombectomy with thrombuster device was done in 26 patients.

None of those who had a primary procedure achieved complete reperfusion by either APS or MPG. Out of the 85 with routine/rescue procedures, complete reperfusion as assessed by TMPG 3 was seen in 11.8% (10/85) and by full APS in 50.6% (43/85) (p ≤ 0.001). Partial (TMPG 1–2) and failed (TMPG 0) reperfusion was demonstrated in 23.5% (20/85), 28.23% (24/85), total 51.76% (44/85) and 36.47% (31/85) respectively. This contrasted with APS assessed partial and failed reperfusion in 32.9% (28/85) and 16.5% (14/85), respectively (p < 0.01). Hence, significantly more patients were adjudged to have been successfully reperfused by the APS methodology than by TMPG scoring: 83.5% (71/85) vs 63.5% (54/85) (p ≤ 0.01).

#### 3.2. NSTEMI (Table 2)

In this subgroup, 36 patients underwent early PCI, within 48 hours while intervention was delayed to between 2 and 7 days of hospitalization in the remaining 102. Thrombectomy was done in 16 patients, 12 being in the early intervention group.

In the early intervention strategy complete reperfusion was indicated by TMPG 3 in 19/36 (52.8%) and by Full APS in 25/36 (69.4%) (p ≤ 0.001) These numbers was significantly greater than partial reperfusion and failed reperfusion by both MPG and APS. Partial reperfusion (TMPG 2) was observed in 22.2% (8/36), minimal reperfusion (TMPG 1) in 13.9% (5/36) and failure to reperfuse (TMPG 0) in only 11.1% (4/36) (p < 0.01 for trend). Similarly, Partial APS was seen in 19.4% (7/36) and failed APS in 11.1% (4/36).
In the delayed intervention subgroup, by TMPG analysis more patients failed to reperfuse or had minimal perfusion, compared to those who had complete or partial perfusion (TMPG 0–25.5% (26/102); TMPG 1–51% (52/102) versus TMPG 2–15.7% (16/102); TMPG 3–7.8% (8/102) (p = 0.01)). However, by APS analysis no difference in perfusion status were found: 30.4% (31/102) failed versus 31.4% 32/102; partial versus 38.2% (39/102) full perfusion (p = 0.43, NS). This contrasted with the early invasive group where 69.4% (25/36) and 19.4% (7/36) showed full and partial APS with failed APS in only 11.1% (4/36) (p < 0.001 for trend). These figures point out that when early invasive strategy is applied in NSTEMI, more patients show complete reperfusion as indicated by full APS. Also in the early invasive strategy, APS identifies more reperfusions vs TMPG alone.

Comparing APS with TMPG in the entire study group, the percentage of patients with complete and partial perfusion as identified by TMPG 2 and 3:38.9% (88/226) was less than that 78.31% (177/226 identified by APS, p < 0.01). TMPG scoring hence appeared to indicate that lesser percentage of patients are reperfused by PCI in ACS and in effect might identify a smaller number of patients at low risk of MACE post procedure. That this might be true has been reflected in the results of clinical outcomes of MACE.

4. Clinical outcomes

Major adverse cardiac events (MACE) were defined as a composite of death, reinfarction or ischemic-driven target vessel revascularization. Reinfarction was defined as elevation of CK-MB enzyme levels three times above its upper limit of normal associated with ischemic symptoms (Table 3).

<table>
<thead>
<tr>
<th>Table 3 – MACE in the APS group.</th>
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<tbody>
<tr>
<td>Failed APS</td>
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<tr>
<td>(n = 49)</td>
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<tr>
<td>Death (5)</td>
</tr>
<tr>
<td>Re Mt (4)</td>
</tr>
<tr>
<td>TVR (8)</td>
</tr>
<tr>
<td>Composite (17)</td>
</tr>
</tbody>
</table>

4.1. Deaths

There were a total of 5 deaths in the present study. Four patients died during hospital stay, three due to persistent heart failure and the one due to probable stent thrombosis. One died suddenly at home on the 22nd post discharge day, with possible stent thrombosis. Of these, 4 occurred in the failed APS group (4/24, 16.7%) compared to none in the full APS category (p = 0.001). One death occurred in the partial APS group (1/82, 1.2%) (p = NS) (Table 3). In contrast, deaths were evenly distributed between grades 0–3 of TMPG, differences not being statistically different.

4.2. Reinfactions

There were a total of 4 clinical reinfarction of which 2 were in the failed APS group (2/24, 8.3%), 1 in the partial APS group (1/24, 1.2%) and 1 in the full APS group (1/120, 0.8%) (p = 0.038). In the TMPG analysis, reinfarction was distributed 2 each in the TMPG 0:3.3% (2/61) and TMPG 2 (2.2% 2/96).

4.3. Clinically driven target vessel revascularization (TVR)

Was done in 8 cases. Of these 5 (62.5%) were in the failed APS group. Incidence of TVR was 0.8% (1/120) in the full APS, 2.4%(2/82) in the partial APS group (p < 0.001; full vs failed APS). In the TMPG distribution, TVR occurred in 3.3% (2/61); 6.3%(2/32); 3.1%(3/96) and 2.7%(1/37), respectively in TMPG categories 0–3, not being statistically different.

4.4. Composite of endpoints

A total of 17 composite endpoints (MACE) were observed in the study. Of these, 64.7% were seen in failed APS. MACE incidence was 1.7%(2/120) in the full APS and this was significantly less than 45.8%(11/24) in the failed APS (p < 0.001) and 4.9%(4/82) in the partial APS groups. Thus, a full APS clearly indicated a good 30 day post procedure outcome. There were no differences in the baseline characteristics of those who had full, partial or failed APS (Table 5).

This was in contrast to MACE occurrence going by post procedure TMPG scoring alone. There was no statistical difference across TMPG 0,1 and 2, but there was a trend toward lower events with better TMPG. Significant differences were noted only between TMPG 2 and TMPG 3 (p = 0.001) (Table 4). The incidence of MACE was 9.8% (6/61); 9.4%(3/32); 7.3%(7/96) and 2.7%(1/37), respectively in the TMPG 0–3 groups.

When APS was estimated using only post intervention TFG and TMPG with a total score of 6 and patients divided into failed (0–3) and full (4–6) APS groups, there was no

<table>
<thead>
<tr>
<th>Table 4 – MACE in the TMPG group.</th>
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<tbody>
<tr>
<td>TMPG 0 (n = 61)</td>
</tr>
<tr>
<td>Death (5)</td>
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<tr>
<td>Re Mt (4)</td>
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<tr>
<td>TVR (8)</td>
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<tr>
<td>Composite (17)</td>
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</table>
Table 5 — Baseline parameters in the three APS groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Failed APS n = 24 (10.6%)</th>
<th>Partial APS n = 82 (36.3%)</th>
<th>Full APS n = 120 (53.1%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.4 ± 11.8</td>
<td>58.2 ± 11.1</td>
<td>55.9 ± 10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>66.7 (16/24)</td>
<td>57.3 (47/82)</td>
<td>66.7 (67/120)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior ACS</td>
<td>12.5 (3/24)</td>
<td>14.6 (12/82)</td>
<td>13.3 (16/120)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>50 (12/24)</td>
<td>53 (44/82)</td>
<td>49.1 (59/120)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20.8 (5/24)</td>
<td>23.3 (22/82)</td>
<td>23 (28/120)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.5 (9/24)</td>
<td>41.6 (34/82)</td>
<td>34.2 (41/120)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>41.1 (1/24)</td>
<td>9.8 (8/82)</td>
<td>5.8 (7/120)</td>
<td>NS</td>
</tr>
<tr>
<td>SBP mmHg</td>
<td>138 ± 21.3</td>
<td>134.2 ± 22.1</td>
<td>136.5 ± 22.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>72.7 ± 15.1</td>
<td>74.8 ± 16.1</td>
<td>74.7 ± 14.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

5. Discussion

Percutaneous coronary interventions (PCI) are the treatments of choice in patients presenting with ACS. Patency of the culprit vessel or the infarct-related artery may not be enough to judge success which will depend more on the prevention of major coronary events both in the hospital and post discharge. Establishment of myocardial perfusion as seen by TMPG is currently the accepted parameter for predicting outcomes after PCI. In the study by Wong et al., TMPG was correlated with NSTEMI. TMPG 0/1 flow both before and after intervention was associated with increased risk of death or myocardial infarction at 6 months. Using the TMPG, Henriques et al. were able to detect a group of patients with reduced myocardial reperfusion despite normal flow in the epicardial infarct-related coronary artery. Patients with TMPG 0 or 1 had a higher mortality compared with patients with TMPG 2 or 3 (13% versus 3%; RR, 4.7; 95% CI, 2.3–9.5; p < 0.001). Also, the combined incidence of death, recurrent myocardial infarction, or revascularization was higher in the group with TMPG 0 or 1 (33% versus 21%; RR, 1.8; 95% CI, 1.1–2.8; p = 0.009). Impaired myocardial perfusion on the angiogram has been associated with greater left ventricular end-diastolic pressure and the presence of overt congestive heart failure on presentation. However, TMPG tends to completely ignore the epicardial flow as earlier determined by TIMI flow grading. There is a bidirectional nature to any causal relationship between epicardial flow and myocardial perfusion, it is likely that after restoration of full epicardial patency, impaired myocardial perfusion may play a major role in reducing antegrade flow in the epicardial artery. To optimize outcomes, both epicardial and microvascular perfusion must be restored to normal.

Gibson et al. in a substudy from TIMI 10B concluded that TMPG post PCI adds additional long-term prognostic information to the conventional epicardial TFG and CTFC. But determining myocardial perfusion after PCI without taking into consideration the status of perfusion prior to the procedure may not be totally predictive of outcomes. With these points in view a single parameter, the APS has evolved integrating pre and post PCI angiographic perfusion at epicardial and micro vascular levels. APS was first investigated in a patient population presenting with ACS and undergoing PCI by Gibson et al. In their study, lower APS was associated with larger infarct sizes and mortality rate by 30 days increased with worsening APS.

In our study, we found a statistically significant correlation between APS and all the three MACE parameters and the composite of all endpoints. As compared to TMPG done post PCI, APS identified more individuals with risk for future events. The incidence of MACE was significantly higher as predicted by failed APS (22.4%) in contrast to that reported in TMPG 0 (9.8%; 0 ≤ 0.01) (Tables 3 and 4).

Also, conversely we looked at APS vs TMPG alone for identifying patients at low risk of events post procedure. Our study found a trend toward lower MACE rate with improvement in TMPG but this was statistically significant only in the TMPG 3 cohort. Demonstration of TMPG 3 identified 37/226 (16%) as having significantly lower MACE. This was significantly less than the 107/226 (47.34%) identified as having low risk for MACE by full APS (p = 0.01) and 177/226 (78.3%) (p = 0.001) when partial APS was also taken into consideration. APS thus predicted low risk for 30 days events better than post procedure TMPG alone. Moreover, while there was a clear cut difference in MACE in the failed vs successful perfusion going by APS scoring, such differences could not be demonstrated on the basis of TMPG assessment alone. MACE incidence was lowest in the complete perfusion (TMPG 3) group and highest in the no perfusion (TMPG 0) group (p < 0.01). However, risk determination is mostly required in the intermediate perfusion groups where no differences were found. As one moved on from TMPG 2 to TMPG 3 the differences significantly jumped (p < 0.001). In the real world scenario, differentiation between these two grades of TMPG may be somewhat blurred, but of vital importance since MACE incidence goes down very significantly from partial to complete perfusion.

This, we propose, can be overcome by the simple scoring system of APS which combines TMPG and TFG before and after PCI and takes care of the minor differences arising out of operator-related interpretation of the angiographic parameters. This combined score not only clearly identifies low risk patients post PCI but also identifies a larger number of such patients versus TMPG measured alone post PCI.

Is combining TMPG and TFG just once after PCI rather than adding scores both before and after PCI, not sufficient to predict MACE? An analysis of our results showed that no significant differences in MACE incidences were evident between failed and successful PCI going by APS scores determined only once after PCI. Failed APS (0–3) and full APS (4–6)
by adding TFG and TMPG after PCI showed a MACE incidence of 8.9% vs 6.4%, respectively; \( p = \text{NS} \).

Short term and long-term clinical outcomes in ACS depend upon the completeness of revascularization. We report an APS which is a combined measure of pre and post TFG plus TMPG scores, as a predictor of risk following a successful PCI. While many earlier studies have advocated the identification of patients with high risk depending on the TMPG status 0–1, our report highlights that APS is superior to the individual measurements in identifying patients at lower risk for early clinical events following intervention.

6. Conclusion

To optimize outcomes, both epicardial and microvascular perfusion must be restored to normal. TMPG which is the favored method of predicting outcomes has the ambiguity of using a single parameter taken at one point in time, and is low on sensitivity to identify patients with good prognosis post PCI. This can be overcome by the simple scoring system of APS which combines TFG with TMPG before and after PCI and takes care of the minor differences arising out of operator related interpretation of the angiographic parameters. APS is a better discriminator of 30 day MACE than TMPG alone or combined TFG with TMPG score taken only after PCI. Also, while most earlier studies with TMPG emphasized on identifying high risk patients depending TMPG status 0–1, we look at APS as a better predictor of low risk as compared to TMPG.

Conflicts of interest

All authors have none to declare.

REFERENCES


