Dual Energy Imaging for Optimisation of P/V Ratios in VP SPECT

Alexander Doruyter (✉ doruyter@sun.ac.za)

Stellenbosch University <https://orcid.org/0000-0001-9294-1737>

Jennifer Holness

University of Cape Town

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Abstract

Purpose

Ventilation-perfusion single photon emission computed tomography (VP SPECT) plays an important role in pulmonary embolism diagnosis. Rapid results may be obtained using same-day ventilation followed by perfusion imaging, but generally requires careful attention to achieving an optimal count rate ratio (P/V ratio) of $\sim 3:1$. This study investigated whether the ratio of counts simultaneously acquired in adjacent primary and Compton-scatter energy windows (E_ratio) on V SPECT was predictive of final normalised perfusion count rate (PCR_{norm}) on P SPECT using [^{99m}Tc]Tc-macroaggregated albumin (MAA), allowing optimisation of P/V ratio.

Methods

Same-day VP SPECT studies acquired using standard protocols in adult patients during a 2-year period were assessed. Studies were included provided they were acquired with correct imaging parameters, and injection site imaging and laboratory records were available for quality control and normalised count rate corrections. Extraction of DICOM information, and linear regression were performed using custom *Python* and *R* scripts. A predictive tool was developed in Microsoft Excel.

Results

Of 643 studies performed, the scans of 343 participants (median age 30.4 years, 318 female) met inclusion criteria. A single outlier with high influence was excluded after an obvious cause was identified. Final analysis of the remaining 342 scans yielded a significant regression equation ($F(1,340) = 1057.3$, $p < .000$), with an adjusted R^2 of .756 and MSE of 0.001089. A prediction tool designed for routine clinic use was developed for predicting final P/V ratio.

Conclusion

The ratio of simultaneously acquired counts in adjacent energy windows on V SPECT is linearly related to perfusion count rate after administration of a known activity of [^{99m}Tc]Tc-MAA. A predictive tool based on this work may assist in optimising the dose and timing of [^{99m}Tc]Tc-MAA administration in same-day studies to the benefit of patients and workflows.

Introduction

The perfusion component of a ventilation-perfusion single photon emission computed tomography (VP SPECT) study is typically undertaken on the same day as, and frequently immediately following the ventilation component. When using technetium-99m (^{99m}Tc)-based radiopharmaceuticals in a same-day imaging strategy (generally recommended, especially to obtain rapid diagnosis of pulmonary embolism) [1], residual ventilation counts contribute to the acquired perfusion images and may obscure perfusion

defects leading to misdiagnosis. While software can perform correction for residual ventilation counts in the final perfusion image, slight differences in radiopharmaceutical distributions, and imperfect co-registration can lead to significant artefacts and it is therefore recommended that the perfusion count rate (PCR – corrected for residual ventilation counts) exceeds the ventilation count rate (VCR) by a factor of at least 3 [2–4]. This is equivalent, when a perfusion SPECT is performed immediately after the ventilation SPECT, of the uncorrected count rate exceeding the VCR by a minimum factor of 4. At the same time, higher ratios may also be considered undesirable since these would require high doses of the perfusion radiopharmaceutical [^{99m}Tc]Tc- macroaggregated albumin ([^{99m}Tc]Tc-MAA), which would result in higher radiation dose, and increased risks posed by the administration of a high number of [^{99m}Tc]Tc-MAA particles. The former is especially relevant in VP SPECT studies performed to diagnose pulmonary embolism (PE) in pregnant or lactating women in whom radiation exposure poses an additional risk; while the latter is relevant especially when administering [^{99m}Tc]Tc-MAA in patients with known or occult disorders of the pulmonary vasculature.

The targeting of an optimal perfusion/ventilation count rate ratio (P/V ratio) is complicated principally by the fact that it is often difficult to quantify the amount of ventilation activity that has been administered in any individual patient. In patients with a large amount of attenuating soft tissue, higher amounts of administered activity may be required to obtain a sufficiently high VCR to guarantee a ventilation SPECT of sufficient quality. Post hoc calculation of administered ventilation activity using knowledge of the imaging system sensitivity alone is not possible due to the frequently significant amount of attenuation by thoracic tissue. While absolute quantification of administered ventilation activity is possible using quantitative SPECT, this remains experimental and requires specialised software and a SPECT/CT system [5]. As a result, the dose and timing of [^{99m}Tc]Tc-MAA administration after the ventilation SPECT is frequently suboptimal, resulting in PCRs that are either too low to achieve an adequate P/V ratio, or the administration of activities exceeding those recommended or required, and thus not meeting the principle of “as low as reasonably achievable” (ALARA).

Using a variety of techniques, it is possible to account for photon attenuation using information from a second, simultaneously acquired Compton scatter window [6]. A linear relationship between the number of photons detected in scatter windows and voxel attenuation coefficients has previously been described [7].

This study aimed to investigate whether a simple ratio of counts acquired in two adjacent energy windows on the ventilation SPECT (E_{ratio}) is predictive of the final perfusion count rate normalised for [^{99m}Tc]Tc-MAA activity (PCR_{norm}) on the perfusion SPECT; and if so, whether such a relationship can be used to develop a simple tool to adjust either the *activity* (dose) of [^{99m}Tc]Tc-MAA administered or the *timing* (or both) of the perfusion SPECT, such that an optimal P/V ratio may be achieved.

Materials And Methods

Participant selection

All patients referred to the Tygerberg Hospital Division of Nuclear Medicine for VP SPECT studies between July 2017 and July 2019 were eligible for inclusion. Only patients with same-day studies (ventilation followed by perfusion) and who were older than 18 years were included in this retrospective analysis. Patients in whom no [^{99m}Tc]Tc-MAA injection site imaging was performed; or for whom the [^{99m}Tc]Tc-MAA dispensing time was not recorded (to correct [^{99m}Tc]Tc-MAA dose for residual counts at administration site, and for decay) were excluded, as were the scans of patients in whom the imaging acquisition differed from the divisional protocol; or in cases in which a repeat SPECT acquisition was performed.

Imaging procedure

Ventilation was performed with the patient lying supine, using a [^{99m}Tc]Tc-Technegas generator (Vita Medical Ltd, Lucas Heights, New South Wales, Australia). After each breath, tubing of the ventilation system was set aside and a Geiger-Müller (GM) detector (Radiation Alert® – Inspector, SE International Inc, Summertown, TN, United States) positioned on the sternum. Technicians were instructed to target an approximate stabilised probe count rate of ~2500 counts per minute (cpm). Immediately after ventilation, SPECT was performed on a dual-head Siemens Symbia SPECT camera (Siemens Healthineers, Hoffman Estates, IL, USA). Acquisition protocols were chosen to match most closely those recommended by Palmer et al [4] – Table 1. All SPECT scans were acquired with a primary energy window centred on a peak of 140 keV ($\pm 7.5\%$); and a symmetrical down-scatter window, centred on a peak of 119 keV, of exactly the same width immediately beneath this. The latter window has been routinely included in VP SPECT acquisitions in the Tygerberg Division of Nuclear Medicine since 2015, at which time image reconstruction software (Hermes Gold 3; Nuclear Diagnostics, Stockholm Sweden) used this data to construct a synthetic attenuation map.

The perfusion study was acquired either immediately after the ventilation study or after a delay to allow for some decay of ventilation counts using ~120 MBq of [^{99m}Tc]Tc-MAA (Pulmocis®, Cisbio). All dispensed [^{99m}Tc]Tc-MAA doses had a radiochemical purity of $\geq 95\%$. Static acquisitions (64 x 64 matrix, 60 seconds, 129.5 – 150.5 keV), using the same LEAP collimator as used for SPECT, were made of the [^{99m}Tc]Tc-MAA injection site to exclude major misinjection and to quantify residual activity in the injection portal. Residual activity in the syringe was not measured.

Data extracted from DICOM files and paper records

From the radiopharmacy and patient scan records, the time [^{99m}Tc]Tc-MAA was dispensed and the activity at dispense time were recorded.

All raw tomographic VP SPECT image data, as well as corresponding injection site images for the period in question were downloaded from the divisional PACS in DICOM format.

A custom script written in *Python* version 3.8.2 [8] using the *pydicom* package version 1.4.2 [9] was used to extract information from the DICOM image and header tags, both to assure compliance with divisional acquisition protocols, and to obtain the necessary image measures for analysis purposes.

Information to ensure consistency of the acquisition protocols included width and centring of the energy windows; scan arc; number of frames; frame duration; and camera and collimator identifiers. Scan order (ventilation followed by perfusion) was also validated by checking scan dates and times.

Measures extracted for analysis purposes included patient name, surname, and folder number (subsequently deidentified); patient gender and date of birth (for demographic purposes); scan dates and times (for decay correction); and total image counts for both energy windows (for tomographic data) or in the primary energy window for the injection site images.

Derived image measures and how they were calculated are summarised in Table 2.

Statistical analysis

A linear regression model of E_ratio and PCR_{norm} was built and tested in *RStudio* version 1.3.1093 [10] using *R* version 4.0.2 [11]. Diagnostic plots were generated using native and *ggfortify* [12] packages. A threshold of $p=0.05$ was considered statistically significant. Calculation of 95% prediction intervals for graphing purposes was performed using the native *predict.lm* function.

Prediction tool

Using the results of the linear regression, and the mean squared error (MSE), a tool to predict final P/V ratio was developed in Microsoft® Excel® for Microsoft 365 MSO (16.0.13127.20620) 64-bit.

Results

Selection of participant scans

A total of 643 studies (ventilation SPECT followed by same-day perfusion SPECT) were identified in the study period. Of these, 22 were of patients under the age of 18 years and were excluded. An additional 199 studies were excluded due to missing injection site image; 1 significant misinjection (83 MBq); 69 due to missing radiopharmacy records ($[^{99m}Tc]Tc\text{-MAA}$ dispense time not recorded); 4 due to incorrect dispense time records (recorded time later than scan time); and 1 due to deviation from the divisional protocol (incorrect collimator used). Four participants had repeat studies (10.1 – 58.6 weeks later), and for these participants, only the first study was included in the analysis. An initial analysis was performed

on 343 imaging studies. One imaging study was retrospectively excluded after it became apparent that it was an outlier with high influence and an obvious cause was identified (details below). The sample size for the final analysis was thus of 342 imaging studies.

Demographics and summary statistics

Of the 342 imaging studies included in the final analysis, 317 were performed in female patients. The median patient age was 30.1 years (IQR: 25 – 37.2 years). Mean A_{sys} was 114.8 MBq (SD: 8 MBq). Mean E_{ratio} was 1.83 (SD: 0.21), and mean PCR_{norm} was 0.313 (SD 0.067). Mean P/V ratio was 4.01 (SD 1.09). A breakdown of the final P/V ratio values in the study sample appears in Table 3.

Linear regression

A simple linear regression was calculated to predict PCR_{norm} , given E_{ratio} . The initial scatter plot and diagnostic charts (Figure 1) identified an obvious outlier (datapoint 223: $x=1.89$, $y=0.62$). Further investigation revealed that the ventilation SPECT in this case had a very high amount of activity outside of the patient which very likely influenced the E_{ratio} value (Figure 2). Given that this observation was both an outlier and highly influential, and because an obvious cause was identified on review of the raw data, this observation was retrospectively excluded.

After exclusion of the outlier, a significant regression equation was found ($F(1,340) = 1057.3$, $p < .000$), with an adjusted R^2 of 0.756 and MSE of 0.001089. After adjusting for any specific camera-collimator sensitivity factor, the relationship to yield a re-normalised (adjusted) perfusion count rate was represented by the following equation:

$$PCR = A \times S \times (0.28(E_{ratio}) - 0.198)$$

where PCR represents the expected perfusion count rate (in cps), for any administered activity (A) of [^{99m}Tc]Tc-MAA (in MBq), re-normalised (adjusted) to account for the user-specific sensitivity of the camera-collimator combination, and predicted by E_{ratio} .

The relevant diagnostic plots for the final regression appear in Figure 3. The final model, including confidence and prediction intervals is plotted in Figure 4.

Prediction tool

The output of the linear regression enables calculation of the prediction interval around y , for any future value of x using the equation:

$$\hat{y} \pm t_{(\frac{\alpha}{2}, n-2)} \times \sqrt{MSE \times \left(1 + \frac{1}{n} + \frac{(x_h - \bar{x})^2}{\sum (x_i - \bar{x})^2}\right)}$$

where $\hat{y}$ is the predicted fitted value of y for a particular value of x ; $t_{(\frac{\alpha}{2}, n-2)}$ represents the two-tailed inverse of the Student's t-distribution with significance level α for number of observations n in the regression dataset; MSE is the mean squared error; x_h is the value of a hypothetical future observation of X ; $\bar{x}$ is the mean value of X in the regression dataset; and $\sum (x_i - \bar{x})^2$ represents the respective values of $\sum (x_i - \bar{x})^2$ in the regression dataset [13].

Using the above formula, a practical tool to predict the final *PVR* (with 90% and 95% prediction intervals) was developed in Excel (Supplementary Materials 1). A video demonstrating practical implementation of the tool is included in Supplementary Materials 2.

Discussion

This study found a linear relationship between the ratio of ventilation counts in the primary energy window and an adjacent Compton scatter window and the final perfusion count rate after the administration of a given dose of [^{99m}Tc]Tc-MAA. Results of the analysis were used to develop a practical, Excel-based tool to predict the adequacy of the P/V ratio in same-day VP SPECT studies, which nuclear medicine practitioners can use to optimise the trade-offs that must frequently be made in these studies.

In a same-day VP SPECT study, the ventilation component is followed (ideally immediately after) by the perfusion component. Different strategies are used to increase the likelihood of obtaining ventilation images that are of sufficiently high diagnostic quality, while still meeting a final target P/V ratio of ≥ 3 , and adhering to recommended [^{99m}Tc]Tc-MAA doses. Most divisions target a specific count rate (e.g. 2000 - 2500 cpm) [14,15] measured using a GM detector after ventilation, and having achieved this, proceed to ventilation imaging. Depending on the count rate on the final ventilation SPECT, centres either proceed immediately with injection of [^{99m}Tc]Tc-MAA under the camera detector, usually checking for or titrating to a four-fold increase in counts, or delay the perfusion component of the study until such a time that ventilation count rate is judged to have sufficiently decayed.

There are several problems with these strategies. Foremost, that the VCR is attenuated by variable amounts of soft tissue. This has the effect that a given activity (e.g. 40 MBq) of administered ventilation agent might result in a very high VCR (in a thin patient with minimal attenuating soft tissue), or a very low count rate (in a patient with more thoracic soft tissue), typically requiring the additional administration of ventilation agent. Very high count rates on the final ventilation study may lead to unnecessary deferment of the perfusion study in the first patient (in whom immediately proceeding with e.g. a 120 MBq dose of [^{99m}Tc]Tc-MAA might in actual fact have been sufficient), or lead to an inadequate P/V ratio in the second patient (who might require e.g. 80 MBq of administered ventilation agent to achieve a target count rate) when their perfusion study is undertaken immediately, even with the maximum recommended [^{99m}Tc]Tc-

MAA dose of 160 MBq [1]. Titrating the dose of [^{99m}Tc]Tc-MAA administered to count rate under the camera is a useful compromise [16] but may require excessive amounts of activity (and particles) with attendant risks. It may be speculated that the difficulties in optimising the trade-offs between dose, count adequacy, sufficient P/V ratio, and reasonable patient turnaround times, are greatest in units caring for patients with wide variability in body habitus. Certainly, these trade-offs are frequently imperfect: a multicentre survey including the results of 286 VP SPECT studies in Germany reported inadequate P/V ratios in 25% of studies [16] which is similar to the findings of the current study, in which 18% of studies did not meet the recommended P/V ratio of >3 .

A P/V ratio that is too high is also problematic. While the optimal P/V ratio is uncertain, it seems unlikely that much additional diagnostic benefit is achieved with ratios above 5 (17 % of cases in the current analysis). While [^{99m}Tc]Tc-MAA is generally accepted as a safe compound, it is not entirely innocuous, with reports of respiratory complications and death when high particle numbers have been administered to patients with underlying pathology of the pulmonary vasculature [17–20]. The risks posed by exposure to low doses of ionizing radiation are more controversial [21,22] but certainly it is reasonable to try and minimise the risks conferred by both particle number and radiation when reasonably achievable.

Most SPECT cameras can be easily configured to simultaneously image two adjacent energy windows. Once the ventilation SPECT is complete, it is a simple matter to perform a quick quality check of the raw data, and to use the perfusion adequacy tool to predict the final P/V ratio. Moreover, this tool allows users to prioritise lower radiation dose or higher scan quality by modelling the impacts of different [^{99m}Tc]Tc-MAA doses and/or delays before performing the perfusion SPECT on the P/V ratio.

This study suffered from several limitations. Firstly, many scans had to be excluded from the analysis due to missing injection site imaging or radiopharmacy records, which affected the final sample size. Secondly, the sample was mostly composed of young (adult), pregnant women which means that caution should be exercised when applying the results to other patient demographics. Similarly, the linear relationship between E_ratio and PCR_{norm} at extreme values of E_ratio was based on only a few observations, and the validity of the linear model at these extremes is less certain. Thirdly, confidence and prediction intervals may have been narrower had this study included additional corrections potentially affecting the accurate calculation of the amount of systemically administered [^{99m}Tc]Tc-MAA (A_{sys}): a) for residual activity in the syringe after administration, and b) for the interval between injection and the perfusion SPECT. The latter limitation is however not expected to be a major contributor to error, given the divisional policy of commencing the perfusion SPECT immediately post-injection. Fourthly, although radiochemical purity of [^{99m}Tc]Tc-MAA was routinely above 95%, variation above this threshold was not accounted for, which may have contributed slightly to error in PCR_{norm} . Finally, an inherent limitation in predicting PCRs is presented by variability in right-left shunting (including physiological shunting) which could not be accounted or corrected for [23].

Conclusion

The expected perfusion count rate for a given dose of [^{99m}Tc]Tc-MAA is linearly related to the ratio of ventilation counts in two adjacent energy windows. This relationship allows for the application of a simple tool to predict and/or optimise the final P/V ratio. In addition to the practice of directly monitoring count rate increases during [^{99m}Tc]Tc-MAA injection, this tool may assist in optimising the trade-offs between study quality, [^{99m}Tc]Tc-MAA dose, and patient turnaround time while still achieving diagnostic quality VP SPECT studies.

Declarations

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Conflicts of interest/Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was approved by the Human Research Ethics Committee of Stellenbosch University (Ref # N20/09/096).

Consent to participate

Due to the low risk of this retrospective analysis, a waiver of informed consent was granted by the Stellenbosch University Human Research Ethics Committee.

Consent for publication

N/A.

Availability of data and material

Regression data are included in supplementary materials. Other non-identifying data are available from the corresponding author on reasonable request.

Code availability

Python and *R* scripts are available from the corresponding author on reasonable request.

Authors' contributions

AD contributed to the study conception and design. Material preparation, data collection and analysis were performed by AD and JH. The first draft of the manuscript was written by AD and both authors commented on previous versions of the manuscript. Both authors read and approved the final manuscript.

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Tables

Table 1 SPECT acquisition parameters

Camera model	Siemens Symbia – dual detector
Collimators	LEAP
Collimators sensitivity (measured)	133 cps/MBq
Matrix	64 x 64
Zoom	1.45
Pixel size	6.8
Primary energy window centre	140 keV
Primary energy window lower threshold	129.5 keV
Primary energy window upper threshold	150.5 keV
Secondary energy window centre	119 keV
Secondary energy window lower threshold	108.5 keV
Secondary energy window upper threshold	129.5 keV
Frames	120
Angle step	3°
Rotation	360°
Frame duration ventilation SPECT	10 sec
Frame duration perfusion SPECT	5 sec

Abbreviations: **LEAP** – Low-energy, all purpose; **keV** – kiloelectron volts; **sec** – seconds.

Table 2 Derived image measures.

Measure (unit)	Formula	Description
E_ratio (arb. unit)*	$E_ratio = \frac{\sum_{i=1}^{120} v1_i}{\sum_{i=1}^{120} v2_i}$	E_ratio was calculated by summing the counts of all projections in the primary energy window of the raw ventilation SPECT data ($v1$), and then dividing the result by the summed counts of all projections in the Compton scatter energy window of the raw ventilation SPECT data ($v2$).
VCR (cps)	$VCR = \sum_{i=1}^{120} v1_i / t1$	The ventilation count rate (VCR) was calculated by summing the counts of all projections in the primary energy window of the raw ventilation SPECT data ($v1$), and then dividing the result by the ventilation SPECT acquisition duration ($t1$).
$PVCR$ (cps)	$PVCR = \sum_{i=1}^{120} p1_i / t2$	The perfusion+ventilation count rate ($PVCR$) was calculated by summing the counts of all projections in the primary energy window of the raw perfusion SPECT data ($p1$), and then dividing the result by the perfusion SPECT acquisition duration ($t2$).
PCR (cps)	$PCR = PVCR - DF.VCR$	The perfusion count rate (PCR) was calculated by first correcting VCR by the relevant decay factor [DF] to account for the interval between ventilation and perfusion SPECTs, and then subtracting the result from $PVCR$.
P/V ratio (arb. unit)*	$\frac{P}{V} = PCR/VCR$	The P/V ratio was calculated by dividing PCR by VCR .
A_{inj} (MBq)	$A_{inj} = DF.ICR/S$	The activity of [^{99m}Tc]Tc-MAA present at the injection site at time of P SPECT (A_{inj}) was calculated by dividing the count rate on the injection site planar static image (ICR), correcting this value by the relevant decay factor [DF] to account for the interval between perfusion SPECT and injection site imaging, and then dividing the result by camera-collimator sensitivity (S).
A_{sys} (MBq)	$A_{sys} = DF.A_{disp} - A_{inj}$	The activity of [^{99m}Tc]Tc-MAA administered systemically at the time of the perfusion SPECT (A_{sys}) was calculated by first correcting the amount of activity at time of dispensing (A_{disp}) by the relevant decay factor [DF] to account for the interval between dispensing and perfusion SPECT, and then subtracting A_{inj} .
PCR_{norm} (arb. unit)*	$p_{rate} = \frac{PCR}{A_{sys}} / S$	The normalised perfusion count rate (PCR_{norm}) was calculated by dividing PCR by A_{sys} , and then dividing the result by the camera-collimator sensitivity (S).

*Reported in Results section.

Table 3 P/V ratio values of the studies included in the analysis.

P/V ratio	Number of Studies (%)
1-2	7 (2%)
2-3	52 (16%)
3-4	114 (34%)
4-5	105 (31%)
>5	56 (17%)
TOTAL	343 (100%)

Figures

Figure 1

Diagnostic plots of initial sample. a Scatter plot of observations in which E_ratio represents the calculated ratio between acquired counts in the primary energy window divided by the down-scatter window on the ventilation study and PCRnorm represents the perfusion count rate per megabecquerel of administered [99mTc]Tc-MAA (cps/MBq), normalised to a camera-collimator sensitivity of 1 cps/MBq. b Chart of standardised residuals identified an obvious outlier (observation 223), which was also shown to be highly influential on c Cooks' distance chart. Investigation of this observation identified an obvious cause (Figure 2), and on this basis the case was excluded and the regression repeated. Images generated in RStudio.

Figure 2

Reconstructed ventilation SPECT of participant 223, exhibiting high amount of extracorporeal radiopharmaceutical (red crosshair), very likely resulting in an unreliable E_{ratio} value. This participant was excluded from the final analysis. Image generated in Hermes Hybrid Viewer PDR 4.0.1 with linear BW inverse colour table, relative scaling.

Figure 3

Diagnostic plots of final sample, exhibiting a linearity of the data, b normality of the residuals, c homogeneity of variance, and d outlier observations and points with high leverage. Abbreviations: lm: linear model; PCRnorm: normalised perfusion count rate; E_ratio: energy window count ratio of the ventilation study. Images generated in RStudio.

Figure 4

Final linear regression of perfusion count rate normalised to 1 MBq of administered $[^{99m}\text{Tc}]\text{Tc-MAA}$, and a camera-collimator sensitivity of 1 cps/MBq (PCRnorm) as a function of the dual energy window count ratio of the ventilation study (E_ratio). Regression line (blue solid line), 95% confidence band (dark grey), and 95% prediction bands (red dashed lines). Image generated in RStudio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary1Perfusionadequacypredictorv1.xlsx](#)
- [Supplementary2explanatoryvideo.mp4](#)