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Brief Communication

Reduction of Respiratory Motion during PET/CT by Pulsatile-Flow Ventilation™ (PFV-PET/CT): A First Clinical Evaluation

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Short Title: Pulsatile-Flow Ventilation™ PET/CT

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Abstract

Rationale: Respiratory motion negatively affects PET/CT image quality and quantitation. A novel pulsatile-flow ventilation (PFV) system reducing respiratory motion (Transrespirator®, Percussionaire®) was applied in spontaneously-breathing patients to induce sustained apnea during PET/CT.

Methods: Four patients (aged 65±14y) underwent PET/CT for pulmonary nodule staging (mean Ø11±7mm, range 5–18mm) 63±3min after ^{18}F-FDG injection. PET/CT was repeated during PFV-induced apnea (≥8.5min), 47±7min thereafter. Anterior-posterior thoracic amplitude, maximal standardized uptake value (SUV_{max}) and SUV_{peak} (mean SUV in 1-cm-diameter sphere) were compared.

Results: PFV-PET/CT reduced thoracic amplitude (–80%), increased mean lesion SUV_{max} (+29%) and SUV_{peak} (+11%), decreased lung background SUV_{peak} (–25%), improved lesion detectability, and SUV_{peak} lesion-to-background ratio (+54%). On linear regressions, SUV_{max} and SUV_{peak} significantly improved (+35% and +23%, $p \leq 0.02$, respectively).

Conclusion: PFV-induced apnea reduces thoracic organs motion and increases lesion SUV, detectability and delineation. This might impact clinical patient management by improving diagnosis, prognostication, monitoring and external radiation therapy planning.

Key Words: PET/CT; High-Frequency Percussive Ventilation®; HFPV®; Respiratory Motion; Pulsatile-Flow Ventilation™.

Introduction

PET/CT has become a major oncologic imaging modality for diagnosis, prognostication, therapy monitoring and radiation therapy planning (*1*). Respiratory motion has significant negative effects on image quality, PET quantification accuracy of lesion activities, fusion accuracy, and lesion volume delineation (*2*). Several advanced PET/CT respiratory-gating techniques have been developed to palliate for thoracic organs motion (*2*). They all have intrinsic limitations, such as increased PET acquisition duration, mixing of several tissue positions in a single bin and difficulties with irregular breathing patterns. In addition not only PET, but also CT should be gated to avoid introducing supplementary attenuation correction and quantification errors (*2*). Today, these techniques are not universally applied and no consensus exists as the best method to compensate for respiratory motion.

High-frequency percussive ventilation (HFPV®) was first designed to promote airway clearance, through "percussive" flow of air. Based on these hygienic effect, HFPV was then developed in inpatient burn units with percussive airflow favoring evacuation of airway debris secondary to inhalation injury (*3*). The physical principle is to deliver high-frequency ventilation (>400/min) in low ventilation cycles (10-30 cycles/min). Clinical experience demonstrated improved lung compliance, oxygenation and ventilation compared to conventional ventilation in intensive care. These benefits extended the indication as salvage modality for acute respiratory distress syndrome with clinical evidence supported by smaller trials. Successive subtidal breath with added high-frequency oscillations to both inhalation and exhalation phase facilitates oxygen diffusion and carbon dioxide removal. We refined this technique to obtain apnea-like respiratory motion stabilization at full inspirium for medical imaging and radiation therapy (*4*). We achieved apneas lasting 8–16min allowing radiation therapy in non-intubated patients (*4*).

We aimed at establishing Pulsatile-Flow Ventilation™ PET/CT (PFV-PET/CT) to suppress respiratory motion and quantify lesion detectability and quantification.

Material and Methods

Patient population

Patients with a pulmonary tumoral lesion deemed treatable by radiation therapy (November 2014–April 2015) were enrolled in this research protocol, which was authorized by the State of Vaud Ethics Committee on Human Research and all patient signed an informed consent form.

F-18-Fluorodeoxyglucose (FDG) PET/CT Acquisition

Images were acquired on a time-of-flight PET/CT (Discovery D690, GE Healthcare, Waukesha, WI) with scatter/point-spread-function recovery corrections, 60min after injecting ^{18}F-FDG 3.5MBq/kg after ≥6-hour fast (PET: 2-min/bed, 47-slices, 256×256-matrix, OSEM 2i×24s; CT: 140 kV, 80-200SmartmA, 0.5/rotation, 3.75-mm thickness). PFV-PET/CT was performed after PFV apparatus installation with a thorax-dedicated

(3-bed) acquisition with identical PET/CT parameters. Anterior-posterior abdomen/chest displacement was monitored with Real-time Position Management™ respiratory gating system (RPM, Varian Medical Systems Inc., Palo Alto, CA).

PFV-PET/CT

The HFPV® technique (*3*) was refined by suppressing the low-frequency cycles to induce sustained "apnea-like" chest stabilization in spontaneously-breathing patients to maintain adequate pO_2/pCO_2 levels without respiratory motion in collaboration with IMAPe® (International Medical Assistance by Percussionaire®, Villeneuve-Loubet, France), distributor of Transrespirator® for Percussionaire® Corporation (Sandpoint, ID). The resulting PFV-apnea successfully supressed normal respiratory motion in volunteers (11.6-min median time) allowing a successful clinical feasibility study in radiation therapy (n=3 patients) (*4*). Patients were conscious non-sedated, non-intubated, with a mouthpiece interface for delivering non-invasive high-frequency ventilation.

Image Analysis

We used an Advantage workstation (ADW4.6, GE Healthcare, Waukesha, WI) and Osirix6.5.2 (Pixmeo, Geneva, Switzerland) to compute standardized uptake value SUV_{max}, SUV_{peak} (mean SUV/∅1-cm sphere), mean lesion SUV using a 42%- SUV_{max}-segmentation threshold ($SUV_{mean\ 42\%}$) with corresponding lesion volume ($Volume_{42\%}$) and total lesion glycolysis ($TLG_{42\%}=SUV_{mean\ 42\%} \times Volume_{42\%}$).

Statistical Analysis

Wilcoxon matched-pairs signed-ranks tests were used for means comparisons and linear regression for assessing PFV-PET/CT changes with Stata 13.1 (StataCorp, College Station, TX) and a $p<0.05$-significance level.

Results

We enrolled 5 patients, but 1 patient refused to undergo PFV-PET/CT, leaving 4 patients to assess (Table 1). PFV-PET/CT could be successfully performed for ≥8.5-min in all patients. Patients did not feel procedure discomfort thanks to two prior 5-min training sessions outside PET/CT scanner performed on a different day (n=3) or same day (n=1). They all kept normal oxygen saturation values ($SatO_2$=95–100% under FIO_2=100%) with intrinsic breathing motion suppressed and the diaphragm stopped in maximal inspiratory position. The anterior-posterior thoracic amplitude greatly diminished with a trend for a statistical significance despite low patient number (Figure 1A, Table 1, Suppl. Figure 1).

PET/CT SUV metrics (Table 2) showed a trend for a +29% higher mean SUV_{max} (Figure 1C) and a –25% lower SUV_{peak} in lung parenchyma, leading to +54% better lesion-to-lung SUV_{peak} ratio (Figure 1D). Linear regression analysis showed that HPV-induced apnea significantly increased SUV_{max} by +35% (p=0.033) and SUV_{peak} by +23% (p=0.006) (Figure 1B).

PET image quality was much improved with reduced blurring, increased lesion SUV, and decreased lung parenchyma activity. For instance, in patient #1 the pulmonary lesion was not seen on maximum intensity projection image (although ^{18}F-FDG uptake was increased in multiplanar reconstructions) (Figure 2A). The lesion became clearly distinguishable in PFV-PET/CT (Figure 2B).

The effect of lesion blurring is seen in patient #2 with two adjacent pulmonary lesions with different ^{18}F-FDG uptake characteristics (Figure 3A-B, Suppl. Figure 3). PFV-PET/CT led to higher SUV values on the cranio-caudal profile (Figure 3C).

In patient #3 (Figure 4A-B), the pulmonary lesion had a large SUV increase while SUV lung parenchyma decreased due to hyperinflation leading to the highest increase in SUV_{peak} lesion-to-background ratio (Figure 1D). ^{18}F-FDG-positive mediastinal lymph nodes (Suppl. Figure 4) presented increased SUV_{max} by PFV-PET/CT (Table 2). The increase in image quality was visible with improved PET contrast in small structures (esophagus, stomach, ribs, aortic wall) (Figure 4, Suppl. Figure 4).

Patient #4 presented a small ∅5-mm pulmonary lesion not visible on PET images in free-breathing conditions (Suppl. Figure 5). PVF-PET/CT rendered it fairly distinguishable on multiplanar reconstructions (+17% SUV_{max} increase, –22% decrease in neighboring lung parenchyma), although it remained not visible on the maximum intensity projection image.

Discussion

PFV-induced apnea was clinically feasible in non-intubated, non-sedated patients for duration lasting ≥8.5-min allowing full-thorax PET acquisitions with decreased respiratory motion and increased lesion SUV_{max}/SUV_{peak}, and improved image quality.

Several studies using time-based methods or deep-inspiration breath-hold show gain in SUV_{max} between gated and non-gated acquisitions in the 21–69% range and 10–23%, respectively (*2*). For instance, Garcia Vincente et al. (*5*) found a major increase in SUVmax (+83%) in their 42-patient population with nodules of 1.2±0.56cm with an older scanner without time-of-flight and point-spread-function recovery; this might explain the relatively larger difference as compared to our study. Many studies have compared mean difference in SUV_{max} due to respiratory-gating, but only Werner et al. have presented results from linear regression between the gated vs. non-gated SUV_{max} (*6*), finding a +11% increase due to gating (y=1.119·x+1.54). Our study led to a larger increase (+35%), showing much promise for increased PET activity recovery.

In a phantom study, Bowen et al. showed that respiratory-gating allowed to recover only 60% of the true motion-free SUV_{max} tumor-to-background ratio, which corresponded to a +14% increase compared to free-moving acquisitions (tumor-to-background=9.0→10.3) and increased another +10% when motion was totally suppressed (tumor-to-background=10.3→11.2=+24% from free-moving) (*7*). Thus, comparing our results with other respiratory-gating studies may not reveal the true potential of the method.

Although breath-hold techniques have been developed with satisfactory results, apnea duration of >30-s are difficult for sick patients. Our PFV-PET/CT is a non-invasive technique achievable in most patients with ≥8.5-min apnea allowing larger exploration fields (e.g., 3 bed positions).

Obviously our feasibility study has several limitations. First, the limited number of patients cannot assess the full potential of this technique due to limited spectrum of lesion size and localization. However, all patients had improvements in image quality, lesion detectability and SUV quantitation. Additionally, the PET visibility of several structures was strikingly improved (ribs, aortic and stomach walls, etc.) and these encouraging preliminary results should lead to further clinical trials in larger patient cohorts.

Second, it is possible that the additional time required for setting-up the PFV apparatus (47±7 min) favorably impacted lesion ^{18}F-FDG uptake, thus participating to SUV increase. Indeed, Tahari et al. demonstrated that delayed acquisition could increase SUL_{max} by 34% alone (*8*), but their delayed time was longer (80 min). In fact, respiratory gating only improved SUL_{max} by another 17%. It is hard to believe that in our study most of SUV_{max} improvement would be due to additional uptake time, as for instance in the same patient (#3), subcarinal (centrally-positioned) lymph node did not change (SUV_{max}=2.5→2.6=+4%), while mediastinal lymph nodes with larger motion increased more (SUV_{max}=2.2→3.0=+35%).

Further PFV-PET/CT applications could be envisioned in other cancers/lesions affected by respiratory motion (breast, chest wall tumors, liver metastases, pancreas, bile duct and gallbladder, esophageal or stomach, splenic, cardiac or kidneys, etc.), for radiation oncology therapy planning (*9*) or for image-guided biopsies in interventional radiology. Further studies could investigate the discriminating capability of PFV-PET/CT for malignant vs. non-malignant lesions or with radiopharmaceuticals other than ^{18}F-FDG. This method would also be directly applicable to PET/MR hybrid imaging, as MR is also influenced by respiratory motion.

Finally, the clinical value of PFV-PET/CT needs to be established in view of existing respiratory-gating technique or delayed acquisition in larger patients cohorts. It can be useful in radiation therapy planning in relation to "percussion-assisted radiation therapy" sharing the same principle, and already demonstrated feasible at our center (*4*).

Conclusion

Pulsatile-Flow Ventilation™ was successfully applied for inducing apnea-like suppression of respiratory motion lasting ≥8.5-min during PET/CT acquisition. This resulted in increased PET image quality, SUV quantitation, and lesion volume delineation. These promising results call for larger cohort studies to establish the clinical value of PFV-PET/CT.

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Tables (max. 2)

Table 1. Patient clinical characteristics

Patient	**#1**	**#2**	**#3**	**#4**
Age (y)	70	79	65	45
Gender	M	M	F	F
Weight (kg)	95	66	47	66
BMI (kg/m2)	33	21	18	24
Lesion size (mm)	18×17×15	7×4×6	12×25×20	5×5×5
Localization	Left upper lobe	Right upper lobe	Right lower lobe	Right upper lobe
Pathology	NSCLC pT1N0M0	NSCLC pT1aN0M0	NSCLC cT2cN0cM0	NSCLC pT1aN0M0
PET/CT	Staging	Staging	Stereotactic body radiation therapy planning	Staging

NSCLC= Non-small cell lung cancer.

Table 2. Patients ^{18}F-FDG PET/CT uptake parameters.

Variable	Free-breathing	PFV-PET/CT	Difference	P-value
Anterior-posterior motion (mm)	21±11	4±2	–80±12%	0.07
SUV_{max} (g/mL)	3.1±1.0	4.0±1.4	+29±12%	0.07
SUV_{peak} (g/mL)	1.9±1.3	2.2±1.6	+11±23%	0.5
$SUV_{mean\ 42\%}$ (g/mL)	1.9±0.5	2.4±1.6	+22±24%	0.14
Metabolic $Volume_{42\%}$ (mL)	2.6±2.4	1.6±1.4	–19±34%	0.6
$TLG_{42\%}$ (g)	5.8±7.6	3.9±3.5	–5±39%	0.99
SUV_{peak} (lung) (g/mL)	0.52±0.05	0.39±0.14	–25±19%	0.14
Lesion-to-lung SUV_{peak} ratio (1)	3.8±2.9	6.8±6.9	+54±41%	0.07
SUV_{max} (patient #2: mediastinal lymph nodes, n=5) (g/mL)	2.7±0.5	3.3±0.78	+23±14%	0.04

Figure Legends

Figure 1. Effect of PFV-induced apnea compared to free breathing on: (**A**) anterior-posterior respiratory motion, (**B**) PET/CT uptake (SUV_{max}, SUV_{peak}), (**C**) relative increase in SUV_{max} and (**D**) lesion-to-lung ratio SUV_{peak}.

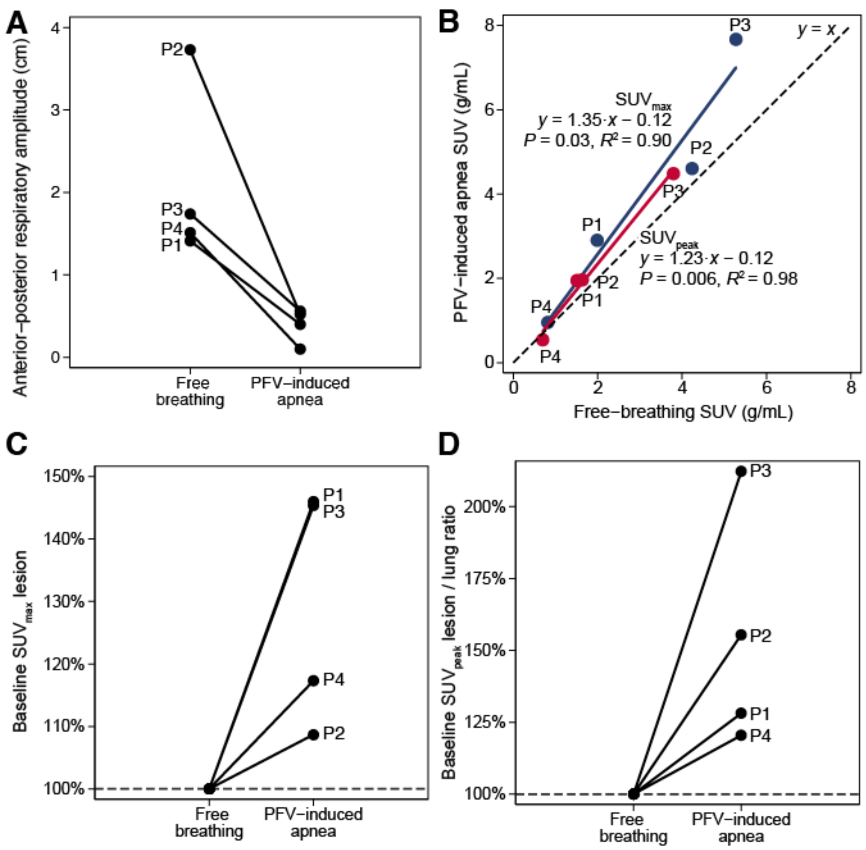


Figure 2. Patient #1: Pulmonary nodule (arrow) with (**A**) free-breathing and (**B**) PVF-induced apnea. The nodule is only visible on maximum intensity projection image in apnea (**A**). More images are available online (Suppl. Figure 2).

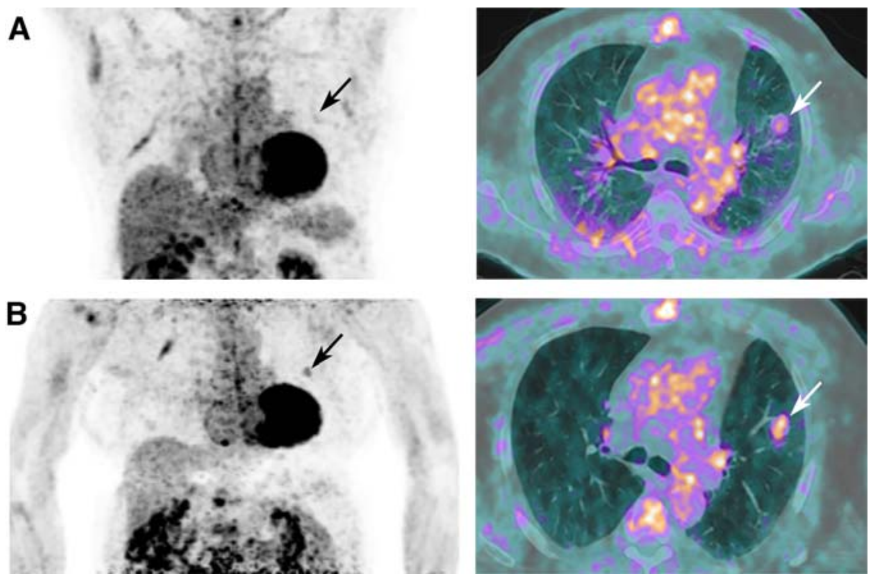


Figure 3. Patient #2: Coronal 2-cm-thick PET slice through tumor in (**A**) free-breathing and (**B**) PFV-apnea with the corresponding SUV pixel values (**C**) along the vertical line through tumor (*arrowhead*). Note higher SUV, lesser blurring and lower SUV in the lung parenchyma in PFV-apnea PET/CT. More images are available online (Suppl. Figure 3).

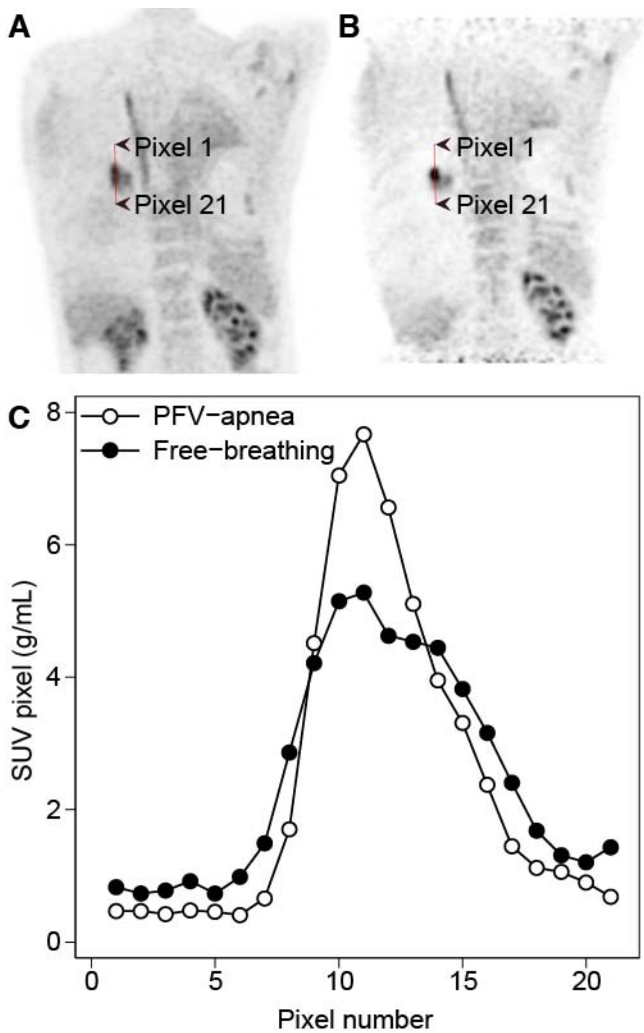
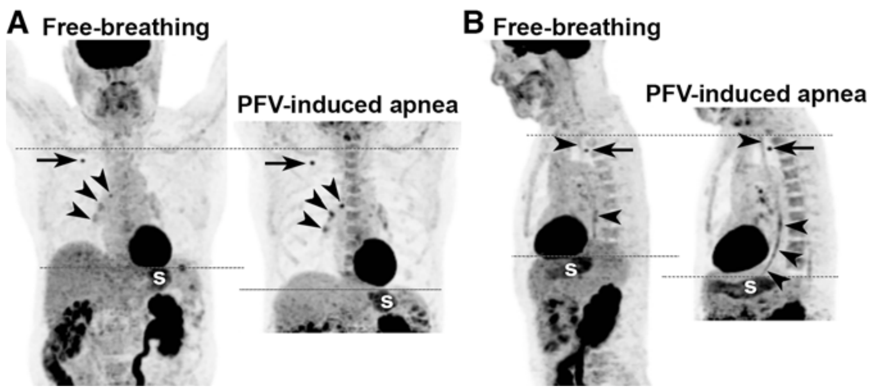


Figure 4. Patient #3: (**A**) MIP with ^{18}F-FDG-positive pulmonary lesion (*arrow*) and mediastinal lymph nodes (*arrowhead*) (*s=stomach*). (**B**) Note the improved lesion-to-background ratio (*arrow*) and better visibility of esophagus (*arrowhead*) in PFV-PET/CT.



Disclosure

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Conflict of Interest: M.V. is an employee of IMAPe®, which distributes the Transrespirator® used in this study, but had no control over the data.

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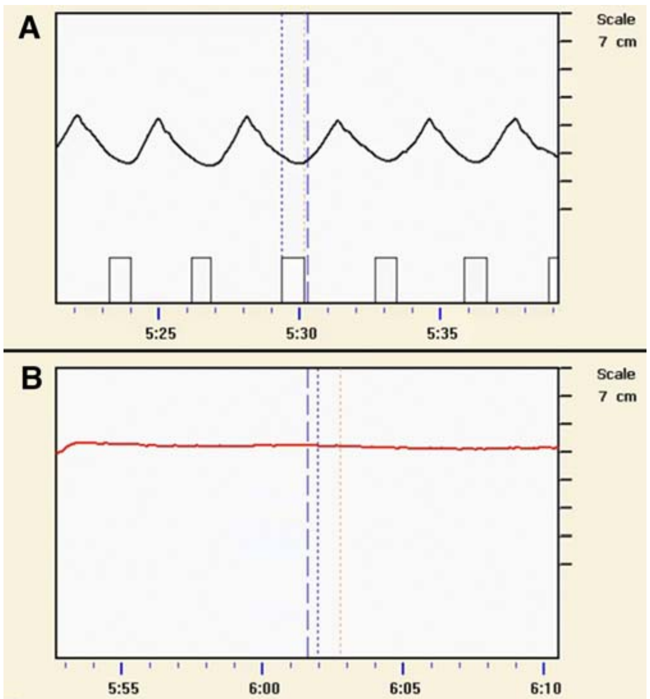
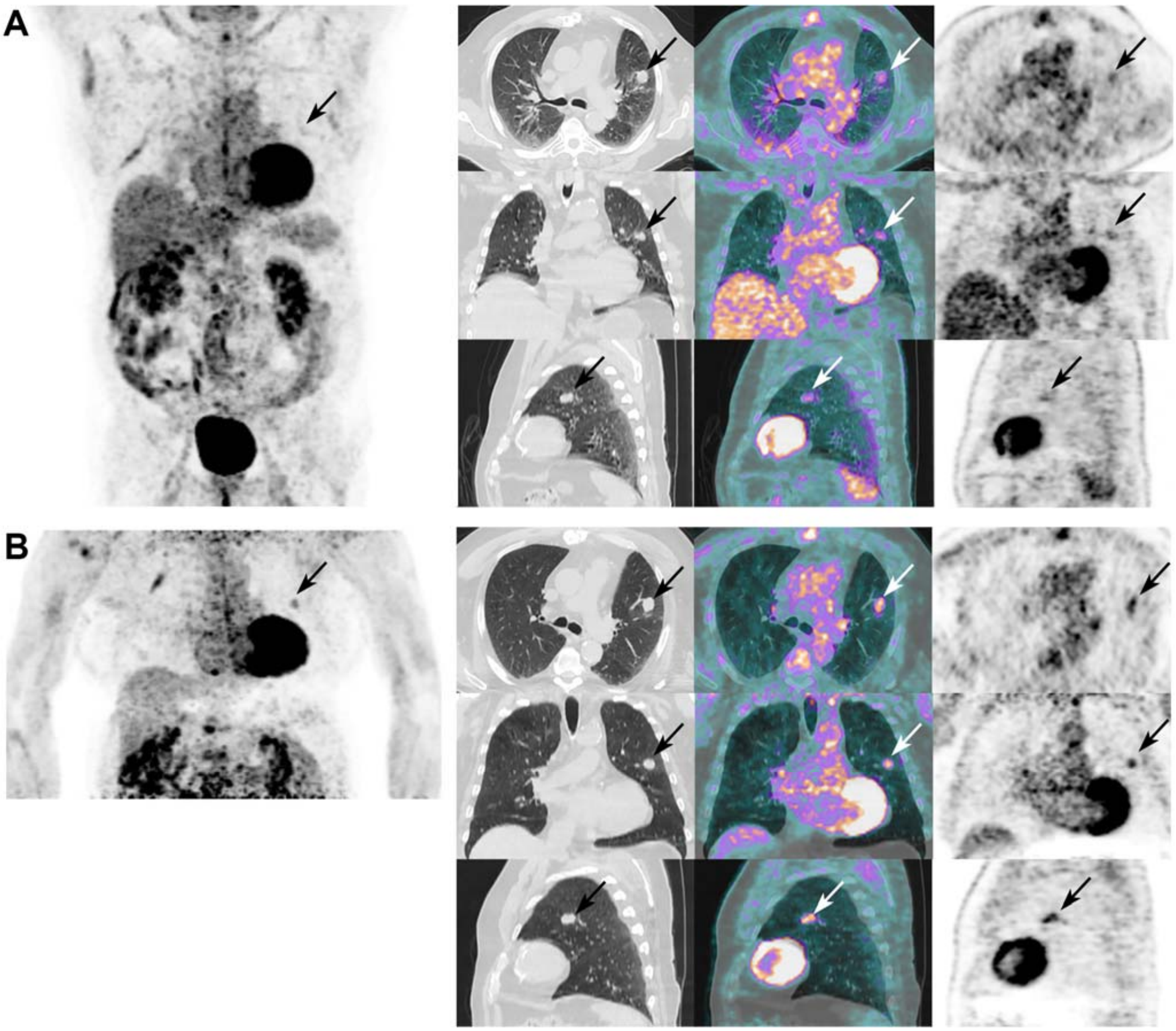
Supplemental Figures (Online Only)

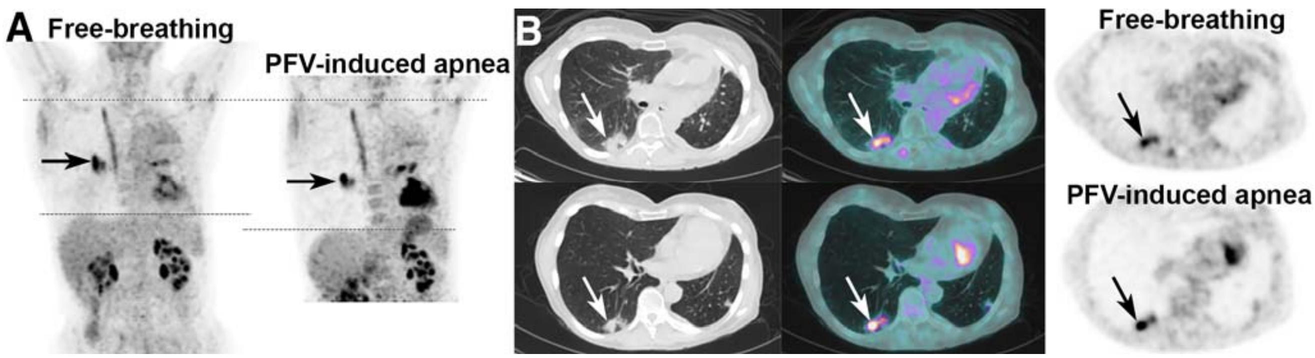
Supplemental Figure 1. Screenshot from the VARIANT RPM signal: (**A**) in free-breathing and (**B**) under PFV-induced apnea conditions (patient #4).



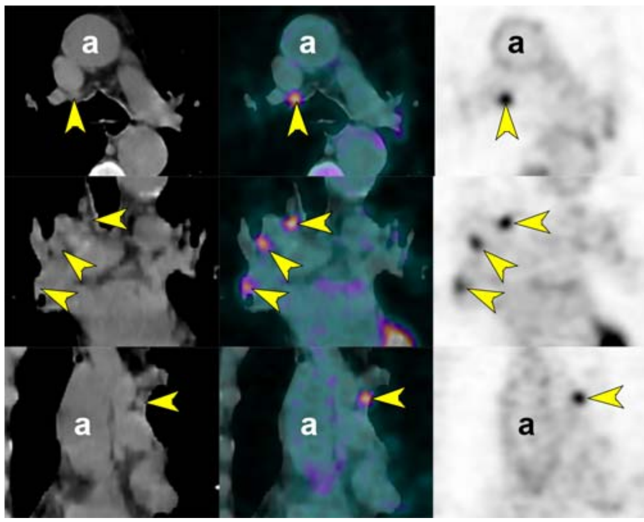
Supplemental Figure 2. Patient #1: Pulmonary nodule (arrow) with (**A**) free-breathing and (**B**) PVF-induced apnea.



Supplemental Figure 3. Patient #2: (**A**) Maximum intensity projection and (**B**) corresponding multiplanar reconstruction images of the pulmonary lesion (*arrow*).



Supplemental Figure 4. Patient #3: Appreciate the finer mediastinum details of PFV-induced apnea PET/CT with multiplanar reconstruction images showing excellent visibility of ^{18}F-FDG-positive lymph nodes (*yellow arrowhead*). Note even the discernable uptake in normal aortic wall (*a=aorta*).



Supplemental Figure 5. Patient #4: (**A**) maximum intensity projection and (**B**) axial/sagittal multiplanar reconstruction images (*b=breast gland*). Pulmonary lesion (*yellow arrowhead*) only visible in PVF-induced apnea PET/CT. Appreciate the finer MIP details (e.g. individual ribs) in PFV-induced PET/CT (**A**).