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ORIGINAL ARTICLE

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Retrospective Study

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ORIGINAL ARTICLE

Basic Study

Effects of muscle fiber orientation to main magnetic field on muscle metabolite profiles for magnetic resonance spectroscopy acquisition

Duanghathai Pasanta, Tipparat Kongseha, Suchart Kothan

ORCID number: Duanghathai Pasanta (0000-0001-6921-2915); Tipparat Kongseha (0000-0002-2416-4902); Suchart Kothan (0000-0001-7390-8878).

Author contributions: Pasanta D, Kongseha T and Kothan S contributed to the conception and design of this study; as well as the acquisition, analysis, and interpretation of all data. These authors wrote drafts of the article and made critical revisions related to the intellectual content of the manuscript and approved the final version of the article for publication.

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Duanghathai Pasanta, Tipparat Kongseha, Suchart Kothan, Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai 50200, Thailand

Corresponding author: Suchart Kothan, PhD, Associate Professor, Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University, 110 Intawaroros Rd., Sripoom, Chiang Mai 50200, Thailand. suchart.kothan@cmu.ac.th
Telephone: +66-53-939213
Fax: +66-53-939207

Abstract

BACKGROUND

Proton magnetic resonance spectroscopy (^{1}H MRS) is a technique widely used for investigating metabolites in humans. Lipids are stored outside the muscle cell are called extramyocellular lipids (EMCL), and lipids stored on the inside of muscle cells are called intramyocellular lipids (IMCL). The relationship between metabolic syndrome and IMCL has been extensively studied.

AIM

To determine the effects of muscle fiber orientations on muscle metabolites using ^{1}H MRS.

METHODS

Chicken muscles were used as the subject in this study. MRS spectra were performed on a 1.5T Magnetic resonance imaging machine (1.5 Tesla Philips Achieva). A single voxel (8 mm × 8 mm × 20 mm) was placed on the chicken extensor iliotibialis lateralis muscle with the muscle fiber oriented at 0°, 30°, 60°, and 90° to the main magnetic field. ^{1}H MRS spectra were acquired using a point-resolved spectroscopy, TR = 2000 ms, TE = 30 ms, and NSA = 256. Metabolites of interest from each orientation to the main magnetic field were compared using Wilcoxon signed-rank test. Differences less than 0.05 were considered to be statistically significant with 95%CI.

RESULTS

The metabolite profiles were different for each orientation of muscle fibers to the main magnetic field. The orientation at 90° was the most different compared to other orientations. The quantity of IMCL and EMCL exhibited statistically significantly changes with impacts at 30°, 60°, and 90° when compared with muscles aligned at 0° to the main magnetic field. Statistical analysis showed statistically significant IMCL (CH_3), EMCL (CH_3), and IMCL (CH_2) at 30°, 60°, and

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90° (P = 0.017, 0.018, and 0.018, respectively) and EMCL (CH_2) at 30° and 60° (P = 0.017 and 0.042, respectively). EMCL (CH_2) at 90° was unable to be measured in this study. The muscle lipids quantified at 30°, 60°, and 90° tended to be lower when compared to 0°.

CONCLUSION
Careful positioning is one of the most important factors to consider when studying ^{1}H MRS metabolites in muscles to ensure reproducibility and uniformity of muscle metabolite spectra.

Key words: Proton magnetic resonance spectroscopy; Metabolite; Muscle fiber orientation; Intramyocellular lipids; Extramyocellular lipids; Magnetic susceptibility

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Core tip: Proton magnetic resonance spectroscopy (^{1}H MRS) is a technique that is widely used for intramyocellular lipids and extramyocellular lipids quantification in muscles, as evidenced in various studies. However, different muscle positions can potentially lead to inconsistency in metabolite quantification and can also impede interpretation of data, which can lead to misinformation. This study reveals that the muscle orientation at 0°, 30°, 60°, and 90° to the main magnetic field significantly affects the metabolite profile and quantification. The metabolite profile changes due to the muscle fiber orientation demonstrate that the positioning potentially causes inaccuracy in ^{1}H-MRS spectrum analysis.

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INTRODUCTION

Proton magnetic resonance spectroscopy (^{1}H MRS) is a technique widely used for investigating metabolites in humans. With insulin resistance, the body stores more lipids in various compartments of organs that normally do not contain fat, such as the liver and muscles. The lipids stored outside muscle cells are called extramyocellular lipids (EMCL), and lipids stored inside muscle cells are called intramyocellular lipids (IMCL). Various studies have shown that IMCL levels are inversely associated with type II diabetes. It is also thought that this relationship is the cause of skeleton muscle insulin resistance and may be an early sign of defective glucose uptake[1,2]. The relationship between metabolic syndrome and IMCL has been studied extensively. Unlike muscle biopsy, ^{1}H MRS is a noninvasive technique suitable for studies that require constant follow-ups and has been popular for use in metabolomics research. Ectopic fat accumulation among various organs, specifically IMCL, is being investigated to gain a better understanding of the pathological mechanisms[3]. The ^{1}H MRS in muscle is usually performed in lower extremity muscles, such as the tibialis anterior, soleus, and gastrocnemius, due to their accessibility for MRI positioning. Nevertheless, much research demonstrates that muscle ^{1}H MRS is influenced by the positioning of the organ of interest[4-6]. It has also been discovered that the orientation of muscle with respect to the direction of the main magnetic field (B_0) affects residual dipolar coupling and bulk magnetic susceptibility on spectra profiles, leading to inconsistencies of metabolite quantification. Hence, it can impede the interpretation and therefore lead to misinformation[7]. Muscle fiber orientation can be determined from dipolar coupling; however, this is an indirect method for measuring muscle fiber orientation[8].

Currently, there are no studies that directly measure muscle alignment to B_0 or how the muscle fibers are aligned to B_0 as it is impossible to measure the exact angle of muscle to B_0 in humans.

The purpose of this study is to determine the effects the muscle fiber angle to B_0 has on the spectrum profile and to obtain muscle lipid quantification without the effect of

muscle contraction. This study used extensor iliotibialis lateralis muscles from chicken thighs as the muscle of interest. Because it is an upper muscle, it is able to give a clear visualization of the muscle fiber alignment to B_0.

MATERIALS AND METHODS

Study subjects

Chicken extensor iliotibialis lateralis muscle was used in this study. A chicken thigh was purchased at local store and was properly skinned, carefully avoiding any muscle tissue. Next, the chicken thigh was placed into a sterile package and stored at 4°C until the time of study.

Data acquisition and analysis

Magnetic resonance imaging with a 1.5 Tesla Philips Achieva (Philips Medical Systems, Best, the Netherlands) equipped with a knee coil was used for the ^{1}H MRS spectrum acquisition. The chicken extensor iliotibialis lateralis muscle fiber alignment was used as the reference point and placed in the middle of the coil, positioned at 0˚, 30˚, 60˚, and 90˚ to B_0. T2-weighted turbo spin echo images in coronal plane and axial plane of muscle were first acquired for voxel localization. Single-voxel point resolved spectroscopy pulse sequence was used for spectrum acquisition with TR = 2000 ms, TE = 30 ms, and NSA = 256 when equipped with automatic shimming. A voxel of size 8 × 8 × 20 mm^3 was carefully placed on the iliotibialis lateralis muscle, carefully avoiding any other muscle fasciae, bulk fat, and air, with verification being obtained from MRI images. Spectra acquisition was repeated 7 times at each angle. All of the spectra in this study were acquired within two hours.

JMRUI version 6.0 β was used for metabolite peak assignment and analysis[9-11]. Spectrum fitting was done by the AMARES algorithm[12] with prior knowledge for line width, and chemical shifts of each peak were obtained from previous studies[13]. Residual water tail was used as the chemical shift reference at 4.72 ppm and then was suppressed with an HLSVD filtering algorithm[14]. The spectrum line shape was estimated with Lorentzian. The zero order phases were estimated by AMARES, and first order phase was fixed at zero with data being truncated by two points for baseline correction. The fitted spectrum showed various peaks of metabolites of interest in the following manner: IMCL (CH_3) at 0.9 ppm, EMCL (CH_3) at 1.1 ppm, IMCL (CH_2) at 1.3 ppm, EMCL (CH_2) at 1.5 ppm, and creatine (Cr) at 3.02 ppm. IMCL and EMCL amplitudes fitted by AMARES were calculated into the ratio per signal intensity of Cr as the internal reference.

Statistical analysis

The data analysis was performed using Origin 8.0 software (OriginLab, Northampton, MA, United States). The calculated results of spectrum fitting at 0°, 30°, 60°, and 90° of muscle fiber orientation to B_0 were compared using Wilcoxon signed-rank test. Statistically significant differences were those less than 0.05, and there was a 95% level of confidence based on this testing. Any metabolite that was undetectable or any measurement that yielded unreliable results by JMRUI was excluded from the statistical analysis.

RESULTS

Chicken muscle spectra were acquired with a carefully placed voxel on the iliotibialis lateralis muscle, avoiding other muscle fasciae, bulk fat, and air, at different angles to B_0 (Figure 1). In previous nuclear magnetic resonance studies, the chicken pectoral muscle tissue showed similar spectra and lipid chemical shifts to that of human muscles[15]. In this study, metabolites of interest were assigned with IMCL (CH_3) at 0.9 ppm, EMCL (CH_3) at 1.1 ppm, IMCL (CH_2) at 1.3 ppm, EMCL (CH_2) at 1.5 ppm, and Cr at 3.02 ppm. This was then quantified with an AMARES algorithm provided by a JMRUI.

The representative spectra profile shown in Figure 2 clearly reveals that muscle spectra were affected by relative muscle fiber orientation to B_0. The spectrum profile at 0° show more well-defined EMCL and IMCL spectra in both the CH_3 and CH_2 groups. The line widths of IMCL and EMCL in both CH_3 and CH_2 groups appear to be broadening, with an increasing angle of muscle alignment to B_0, resulting in overlapping peaks. Additionally, the spectra at 30°, 60°, and 90° appeared to have smaller signal intensity and higher noise when compared to the spectra from 0°, as they were multiplied by a factor of 2. However, Cr at 3.02 ppm remained unaffected

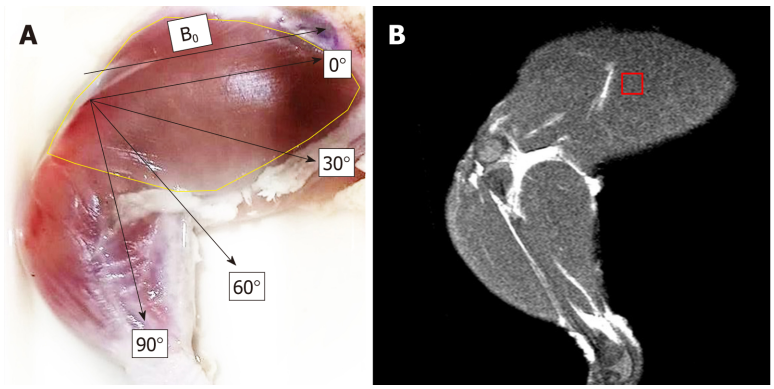

Figure 1 Chicken's extensor iliotibialis was used to perform muscle quantification for muscle metabolites by proton magnetic resonance spectroscopy. A: Skinned chicken thigh showing the extensor iliotibialis lateralis muscle fiber orientation (in the yellow marked area) at various angles (0°, 30°, 60°, and 90°) with regard to the main magnetic field (B_0); B: T2-weighted turbo spin echo MRI images show areas of proton magnetic resonance spectroscopy voxel placement. B_0: Main magnetic field direction.

at every angle. The spectrum profile of orientation at 90° was the most different compared to other orientations. Figure 3 shows the muscle spectrum at 30°, 60°, and 90° subtracted by the baseline at 0°, which revealed drastically different spectrum profiles with alterations in each angle of muscle fiber from the residual form spectra subtraction.

The AMARES algorithm with prior knowledge was performed by spectrum fitting into individual metabolites. Figure 4 shows that the quantification results obtained for EMCL (CH_2) at 1.5 ppm were undetectable for any spectra obtained from 90° orientation and that EMCL (CH_2) was undetectable from 2 spectra at 60°. It appears likely that the spectrum peak broadening made it difficult to differentiate metabolite peaks. The IMCL (CH_3), EMCL (CH_3), IMCL (CH_2), and EMCL (CH_2) were then calculated into a ratio to Cr as the internal reference in each spectrum acquired. The Wilcoxon signed-rank test was used for statistical analysis of lipid ratios to Cr at 0° and to other angles with *P*-values < 0.05. Lipid ratios to Cr were significantly different when comparing spectra at different orientations to 0° (Table 1). However, at 90°, the EMCL (CH_2) peak could not be determined and was excluded from statistical analysis. EMCL and IMCL ratios to Cr were normalized by the mean lipid ratio at 0° to access the differences in ratios when compared to the relative muscle fiber orientation at 0°. The bar graph in Figure 5 demonstrates that the lipid ratios at different angles tended to be lower when compared to lipid ratios obtained at 0°. The comparisons between 0° and at 30°, 60°, and 90° were performed with Wilcoxon signed-rank test and were found to be significantly different from EMCL and IMCL ratios that were obtained from orientations at 0° in every muscle orientation (*P*-value < 0.05).

DISCUSSION

Muscle ^{1}H MRS spectra are known for their unique characteristics, such as dipolar coupling and bulk magnetic susceptibility. Bulk susceptibility was observed to be involved with separation of the EMCL and IMCL peaks, while residual dipolar coupling influenced the resonance of Cr and phosphocreatine. Both dipolar couplings and bulk magnetic susceptibility are orientation dependent. The dipolar coupling effect the aqueous metabolite, while the bulk magnetic susceptibility effects are seen on orientation-dependent structures such as EMCL.

Bulk magnetic susceptibility is an effect that depends on orientation and tissue type, causing nuclei to differently experience the magnetic fields from the external B_0[16]. Our study has shown that the effects of bulk magnetic susceptibility are caused by orientation with B_0. The IMCL and EMCL qualification was affected by the muscle orientation to B_0. Bulk magnetic susceptibility plays an important role in differentiating IMCL and EMCL resonance peaks, and causes wider spectrum bands, leading to shifts of resonance peaks that can affect the EMCL resonance. The results of the EMCL/Cr ratios in this study appear to be consistent with wider standard deviation (SD) values that are obtained when compared to IMCL/Cr taken from the same angle to B_0.

In this study, the spectra obtained at the other angles appear to have smaller

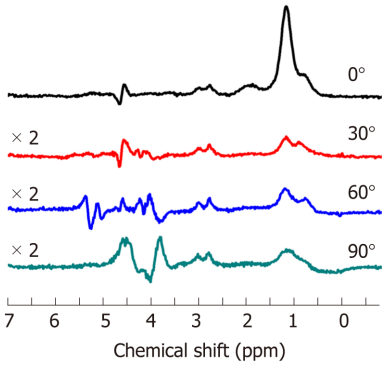

Figure 2 Original proton magnetic resonance spectroscopy spectra at different angles. Muscle spectra at 0° are shown with spectra oriented at 30°, 60°, and 90° multiplied by a factor of 2. The spectrum at 0° showed the most-well defined lipid peaks IMCL (CH_3), EMCL (CH_3), IMCL (CH_2), and EMCL (CH_2). EMCL: Extramyocellular lipids; IMCL: Intramyocellular lipids.

amplitudes when compared to those taken at 0°. Cr is able to pass through cell membranes and therefore is not affected by muscle alignment with the main magnetic field. EMCL is more affected by positioning because of the EMCL environment, which is attached to muscle fiber, and because it is orientation dependent. IMCL can rotate in muscle cytosol in an aqueous state and can therefore average bulk magnetic susceptibility effects[16,17]. In this study, spectrum profiles were different for each orientation of muscle fibers to the main magnetic field. The results suggest that the ^{1}H MRS spectrum was affected not only by pennation angle, as observed in earlier studies[5] but also by the relative muscle alignment to B_0.

Any prior knowledge concerning AMARES algorithms is known to improve metabolite quantification, but it also potentially causes error if the spectrum that was fitted is not a typical spectrum profile. A possible explanation for these results may be because the prior knowledge in the algorithm was obtained from typical human muscle spectrum, while spectrum profiles taken from various positions and orientations of muscle will tend to have peaks that are overlapped, and therefore are almost indistinguishable. This is particularly true for IMCL and EMCL resonance frequencies that were affected by bulk magnetic susceptibility.

These changes in spectrum profiles lead to inaccuracies in metabolite quantification. Different positions with the same qualification algorithms can lead to inaccuracies in metabolite quantification as well. This phenomenon occurs because prior knowledge and the metabolite qualification of metabolites was taken from typical orientations or from a muscle that almost parallels the main magnetic field, such as the tibialis anterior. It is impossible and unlikely to obtain a typical spectrum or prior knowledge from each and every angle. Additionally, the metabolites need to be studied in various muscles for various reasons, especially in deep muscles that are difficult to biopsy. It is important to set a universal standard for muscle orientation in ^{1}H MRS or to obtain a typical spectrum for each muscle of interest to reduce any potential errors and to increase reproducibility.

However, this study observed only small changes from Cr at 3.02 ppm, which was possibly caused by the group rotation of a Cr methyl group that averages these effects out. While phosphocreatine peaks occurred at 4.1 ppm, there were no splitting peaks from any residual dipolar coupling effects. In agreement with previous studies, the residual dipolar coupling vanished after 1-2 h postmortem. This was approximately the same time at which phosphocreatine depletion occurred from energy failure[18]. Our results demonstrated that bulk magnetic susceptibility may play a vital role in the separation and qualification of IMCL and EMCL, without the effects being caused from muscle contraction and residual dipolar coupling.

This present study also indicates the effects of muscle orientation on ^{1}H MRS spectrum data acquired from clinical field evidence and from other species. These results agree with the findings of other studies[18] in that bulk magnetic susceptibility is not exclusively seen in human muscles but is also found in both other mammals and poultry. This tendency occurs even when considering any observed bulk magnetic susceptibility that persists even for postmortem ^{1}H MRS muscle spectra. A limitation of this pilot study that needs to be acknowledged is that the sample size is relatively small, and data were acquired from chickens with no diet control prior to the study. Additionally, there have been no previous studies done on any of the factors that affect IMCL and EMCL levels in chickens. Furthermore, prior knowledge for AMARES algorithms was obtained from human muscles, which can potentially

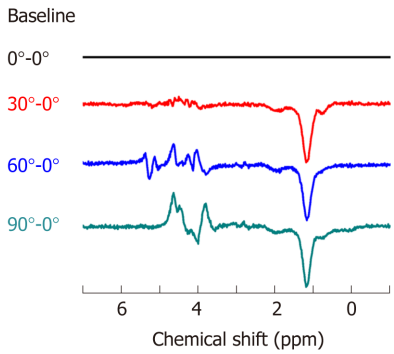

Figure 3 Muscle metabolite spectra at 30°, 60°, and 90° subtracted from baseline set at 0°. Muscle spectra at 30°, 60°, and 90° without multiplied factors are subtracted from spectrum baseline at 0°.

cause quantification errors.

After taking these variables into account, these findings confirm previous findings and provide additional evidence suggesting that muscle spectra can be affected by the relative muscle orientation to the main magnetic field. Taken together, these findings indicate that these variables of muscle orientation must be taken into consideration. There are limitations in this study, such as the small number of samples and the small size of chicken muscles compared to human muscle. In conclusion, the metabolite profile changes are due to the muscle fiber orientation, which demonstrates that positioning potentially causes inaccuracies in ^{1}H-MRS spectrum analysis.

Table 1 The median (25th-75th percentile) values of IMCL (CH_3), EMCL (CH_3), IMCL (CH_2), and EMCL (CH_2) ratios to creatine with the muscle positioned at 0°, 30°, 60°, and 90° to the main magnetic field

Angle	Metabolite							
	IMCL (CH_3), 0.9 ppm	*P* value	EMCL (CH_3), 1.1 ppm	*P* value	IMCL (CH_2), 1.3 ppm	*P* value	EMCL (CH_2), 1.5 ppm	*P* value
0°	1.44 (1.36-1.47)	-	4.25 (4.22-5.35)	-	2.96 (2.53-2.99)	-	3.08 (2.09-3.46)	-
30°	0.80 (0.77-0.81)	0.017[a]	1.23 (1.16-1.33)	0.017[a]	0.55 (0.46-0.60)	0.017[a]	0.28 (0.04-0.44)	0.017[a]
60°	1.15 (0.86-1.19)	0.018[a]	2.03 (1.69-2.08)	0.018[a]	0.77 (0.68-0.91)	0.018[a]	0.04 (0.04-0.11)	0.042[a]
90°	0.64 (0.62-0.64)	0.018[a]	1.29 (1.27-1.32)	0.018[a]	0.30 (0.72-0.31)	0.018[a]	-	-

The *P*-value shows the comparison between the metabolite ratios to creatine at 0° *vs* the different angles, as determined by Wilcoxon signed-rank test (n = 7). Data are expressed as medians (25th-75th percentiles).
[a]*P*-value < 0.05, significantly different.
EMCL: Extramyocellular lipids; IMCL: Intramyocellular lipids.

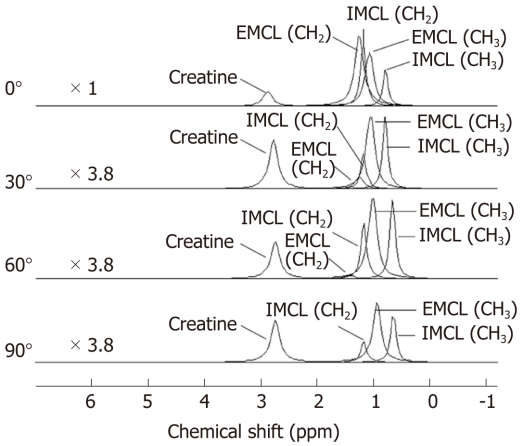

Figure 4 Metabolites identified by AMARES algorithm. Metabolites are shown in the following quantities: IMCL (CH_3) at 0.9 ppm, EMCL (CH_3) at 1.1 ppm, IMCL (CH_2) at 1.3 ppm, EMCL (CH_2) at 1.5 ppm, and creatine at 3.02 ppm. At 30°, 60°, and 90°, spectra were shown by a factor of 3.8. Spectrum of muscle positioned at 90° to the main magnetic field was unable to be identified for EMCL (CH_2) at 1.5 ppm. EMCL: Extramyocellular lipids; IMCL: Intramyocellular lipids.

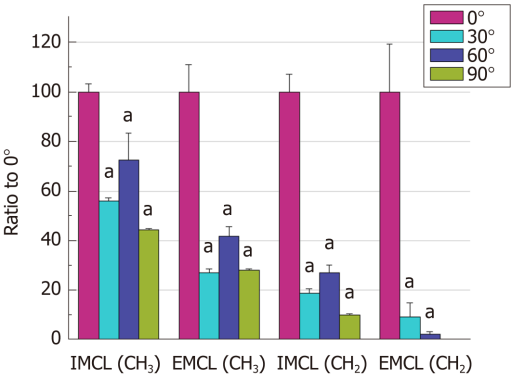

Figure 5 Metabolites at different angle ratios to muscle metabolite at 0°. Each lipid (IMCL (CH_3), EMCL (CH_3), IMCL (CH_2), and EMCL (CH_2)) was calculated as a ratio to creatine and then was normalized with the average of lipid/Cr ratio set at 0°. At 30°, 60°, and 90°, there was a tendency for the ratio to decrease when compared to 0°. The comparisons between 0° and the different angles were performed using Wilcoxon signed-rank test with [a]*P*-value < 0.05 being significantly different. Cr: Creatine; EMCL: Extramyocellular lipids; IMCL: Intramyocellular lipids.

ARTICLE HIGHLIGHTS

Research background

Proton magnetic resonance spectroscopy (^{1}H MRS) is a technique widely used for investigating metabolites in humans. Lipids that are stored outside the muscle cell are called extramyocellular lipids (EMCL), and lipids stored on the inside of muscle cells are called intramyocellular lipids

(IMCL). The relationship between metabolic syndrome and IMCL has been extensively studied. However, muscle position in relation to the main magnetic field can affect spectra profiles, leading to inconsistency of metabolite quantification, which can then lead to misinterpretation.

Research motivation

There is no current study that has directly measured muscle alignment to the main magnetic field or how the muscle fibers are aligned between studies, as it is impossible exactly measure the angle of muscle relative to the main magnetic field in humans.

Research objectives

To determine the effects of the muscle fiber angle to the main magnetic field for obtaining spectrum profiles and muscle lipid quantification without the effects of muscle contraction. This study used extensor iliotibialis lateralis muscles taken from the thigh of a chicken as the muscle of interest. Since it is the uppermost muscle, it provides a clear visualization of the muscle fiber alignment related to the main magnetic field.

Research methods

Chicken extensor iliotibialis lateralis muscles were used as the muscle of interest in this study. Magnetic resonance imaging (1.5 Tesla Philips Achieva) was used for the ^{1}H MRS spectrum acquisition. The chicken extensor iliotibialis lateralis muscle fiber alignment was used as the reference and was place in the middle of the coil, positioned at 0˚, 30˚, 60˚, and 90˚ to the main magnetic field. Single voxel Point Resolved Spectroscopy pulse sequence was used for spectrum acquisition, having a voxel size of 8 mm × 8 mm × 20 mm. It was carefully placed on the iliotibialis lateralis muscle. Spectra acquisition was repeated 7 times for each angle. JMRUI version 6.0 β was used for metabolite peak assignment and analysis. Spectrum fitting was done by an AMARES algorithm with prior knowledge. The fitted spectrum showed various peaks of metabolites of interest in the following manner: IMCL (CH_3) at 0.9 ppm, EMCL (CH_3) at 1.1 ppm, IMCL (CH_2) at 1.3 ppm, EMCL (CH_2) at 1.5 ppm, and Cr at 3.02 ppm. IMCL and EMCL amplitudes fitted by AMARES were calculated into the ratio per signal intensity of Cr in each spectrum as the internal reference. The results of spectrum fitting at 0°, 30°, 60°, and 90° of muscle fiber orientation to the main magnetic field were compared using Wilcoxon signed-rank test.

Research results

The results showed that the metabolite profiles in each orientation of muscle fiber to the main magnetic field were different. The orientation at 90° was the most different compared to the other orientations. The quantity of muscle metabolites was statistically significantly changed at 30°, 60°, and 90° of muscle fiber relative to the main magnetic field when compared to 0° relative to the main magnetic field. Statistical analysis showed statistically significant differences for IMCL (CH_3), EMCL (CH_3), IMCL (CH_2) at 30°, 60°, and 90° (P = 0.017, 0.018, and 0.018, respectively) and EMCL (CH_2) at 30° and 60° (P = 0.017 and 0.042, respectively). EMCL (CH_2) at 90° was unable to be measured in this study. Furthermore, the muscle lipids quantified at 30°, 60°, and 90° tended to be lower when compared to 0°. The metabolite profile changed due to the muscle fiber orientation, indicating that positioning potentially causes inaccuracies in ^{1}H-MRS spectrum analysis.

Research conclusions

This study has determined that the basic muscle orientations to the main magnetic field can and do affect ^{1}HMRS spectrum profiles and quantification. Muscle orientation is often treated with less care in studies on ^{1}H MRS. These metabolite profile changes are due to the muscle fiber orientation, which demonstrates that the positioning potentially causes inaccuracy in ^{1}H-MRS spectrum analysis.

Research perspectives

^{1}H MRS practitioners and users need to be especially careful when positioning any muscles or any organs of interest in order to reduce error, to be able to compare spectrum results across various institutions and to ensure reproducibility and uniformity.

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ORIGINAL ARTICLE

Retrospective Study

Extravascular findings during upper limb computed tomographic angiography focusing on undiagnosed malignancy

Romman Nourzaie, Jeeban Das, Hiba Abbas, Narayanan Thulasidasan, Panos Gkoutzios, Shahzad Ilyas, Leo Monzon, Tarun Sabharwal, Steven Moser, Athanasios Diamantopoulos

ORCID number: Romman Nourzaie (0000-0003-4306-738x); Jeeban Das (0000-0001-7619-4241); Hiba Abbas (0000-0002-8383-2747); Narayanan Thulasidasan (0000-0001-6396-3881); Panos Gkoutzios (0000-0002-7426-790X); Shahzad Ilyas (0000-0002-9043-9425); Leo Monzon (0000-0002-2284-6424); Tarun Sabharwal (0000-0002-9659-256X); Steven Moser (0000-0003-1764-1720); Athanasios Diamantopoulos (0000-0001-9970-0522).

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Romman Nourzaie, Jeeban Das, Hiba Abbas, Narayanan Thulasidasan, Panos Gkoutzios, Shahzad Ilyas, Leo Monzon, Tarun Sabharwal, Steven Moser, Athanasios Diamantopoulos, Department of Interventional Radiology, Guys' and St. Thomas' NHS Foundation Trust, London SE17EH, United Kingdom

Corresponding author: Athanasios Diamantopoulos, MD, PhD, EBIR, Department of Interventional Radiology, Guys' and St. Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, United Kingdom. athanasios.diamantopoulos@gstt.nhs.uk
Telephone: +44-271-887188-89482
Fax: +44-271-887188-89483

Abstract

BACKGROUND

Computer tomography angiography (CTA) has been an established method for diagnostic vascular disease of lower limbs. Recently, the method is widely used for diagnosis of vascular pathologies in the upper limbs too. It also has increased the possibilities of this scans being reviewed by no specially trained radiologists. This increases the risk of incidental non vascular findings to be missed or misinterpreted. The study is focusing in the frequency of extravascular incidental finding (EVIF) and highlights the importance for both the reporting radiologist and the referring physician recognizing the frequency of EVIFs.

AIM

To analyse the frequency of EVIF identified on computed angiography (CT) of the upper limb.

METHODS

A total of 1383 CT angiographic studies of the peripheral arterial system were performed between August 2015 and August 2017. All upper limb CTAs (n = 79) were retrospectively reviewed for the presence of non-vascular incidental findings within the chest, abdomen/pelvis, musculoskeletal system or head and neck. These EVIFs were subsequently grouped into 3 categories based on clinical significance. EVIFs of immediate clinical relevance were included in category A, findings considered indeterminate but most likely benign were placed in category B, while incidental findings of no clinical significance were included in category C.

RESULTS

Complete imaging datasets were available in 74/79 (93.7%). Patient

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demographics included 39 (52.7%) females and 35 (47.2%) males with a mean age of 59 ± 19.5 years (range 19-93 years). A total of 153 EVIFs were reported in 52 patients (70.3%). Of these, 44 EVIFs (28.7%) were found in the chest, 83 (54.2%) in the abdomen, 14 (9.2%) in the musculoskeletal system and 9 (5.8%) in the head and neck. Thirteen EVIFs (8.4%) identified in 11 patients were noted to be of immediate clinical significance (Category A), 50 EVIFs (32.3%) were identified in 20 patients and were considered indeterminate but most likely benign, while the remaining 91 EVIFs (59.5%) identified in 21 patients were determined to be of no clinical significance (Category C). One index case of malignancy (1.3%) and four cases of new disseminated metastatic disease (5.4%) were identified.

CONCLUSION
Our study of upper limb CTA examinations demonstrated a frequency of 8.4% for extravascular incidental findings of immediate clinical significance. We highlight the importance for both the reporting radiologist and the referring physician of the need to recognize the frequency with which EVIFs are identified in the upper limb peripheral arterial system and of the necessity for further clinical and imaging work-up.

Key words: Extravascular incidental findings; Computed angiography; Upper limbs; Arterial; Extravascular findings

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Core tip: We retrospectively analysed 79 upper limb computer tomography angiographys for extravascular incidental findings (EVIFs). These were grouped into 3 categories based on clinical significance, category A (immediate), category B (indeterminate) and category C (no clinical significance). A total of 153 EVIFs were reported in 52 patients. Of these 13 EVIFs (8.4%) were Category A, 50 EVIFs (32.3%) were Category B, while 91 EVIFs (59.5%) were Category C. One index case of malignancy (1.3%) and four cases of new disseminated metastatic disease (5.4%) were identified. This highlights the importance for both the reporting radiologist and the referring physician to recognize the frequency of EVIFs.

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INTRODUCTION

Invasive and cross-sectional arterial phase imaging of the upper extremities are performed less frequently in comparison with lower limb or "run-off" computer tomography angiography (CTA)[1]. Indications for CTA of the upper limb include trauma, suspected upper limb ischaemia, preoperative planning prior to reconstructive surgery or haemodialysis access, or as follow-up post open surgical or endovascular arterial procedure[2].

Digital subtraction angiography (DSA) has conventionally been used as the preferred imaging modality for the upper limb arterial vasculature. However, recent developments and improvements in image acquisition and spatial resolution with multi-detector computed tomography (MDCT), combined with its inherently less-invasive nature, has resulted in CTA becoming the first-line investigation for upper limb arterial pathology[2-4].

For investigation of arterial steno-occlusive disease, CTA has been demonstrated similar diagnostic capabilities compared to DSA, as well as reduced cost, better patient tolerance and the ability to image the extravascular anatomy[2].

The discovery of extravascular incidental findings (EVIFs) can be considered an added advantage of cross-sectional arterial phase imaging. Incidental findings

discovered on CT are defined as an unforeseen pathology encountered in a patient being scanned for another indication. In the case of CT angiography, EVIFs are becoming ever more frequently encountered in daily clinical practice, especially with the exponential proliferation of CT imaging and the gradual phasing out of DSA as a first-line modality for peripheral arterial disease and acute emergent arterial imaging.

CTA offers the possibility of identifying potentially life-threatening or life-shortening pathologies and providing improved health outcomes for patients[5]. EVIFs and their clinical relevance have been well described in CT imaging of the aorta and lower-limb arterial system[5-7], CTA for EVAR planning[8], aortic dissection[9] and CTA of the head and neck[10]. The frequency and significance of EVIF on CTA of the upper limb, however, has yet to be described.

The purpose of this study was to report the frequency and more importantly the clinical relevance of extravascular lesions in patients undergoing upper limb CTA, including the frequency of index cases and progression of known cancer cases.

MATERIALS AND METHODS

Patient selection and demographics

Institutional review board review was obtained for this retrospective study (approval number: 7669, 21/09/2017). Radiology reports, digital medical records and 1383 CTA datasets of the peripheral arterial system performed between August 2015 and August 2017 at Guys and St Thomas hospitals were identified.

Peripheral CTAs imaging the upper limbs were included in the study. Patients with incomplete imaging datasets were excluded. Data on patient demographics, study indication and EVIF were reviewed. Those with significant EVIFs were reviewed to determine their clinical outcome

CT image acquisition and technique

Patients were placed supine with the extremity of interest placed above the head, palm ventral and fingers extended and straightened. CT imaging was performed with a 128 slice MDCT scanner (Siemens Somatom Definition), using bolus tracking software used to trigger intravenous contrast injection (Omnipaque 350, GE Healthcare) at a rate of 4-5 mL per second, followed by saline flush. Images were obtained using a kV between 100-120 with a delay of 20-40 s.

Standard of reference

Radiology reports, digital records, radiological information systems (RIS) records, laboratory and procedure reports were reviewed where available to confirm the presence of pre-existing malignancy and all prior imaging studies were used as the standard of reference (SOR).

Data analysis

One consultant interventional radiologists (15 years of clinical experience) and one radiology IR fellow (6 years of clinical experience) examined all upper limb CTAs and reviewed digital reports for EVIFs. All incidental findings were compared to the SOR and subsequently grouped into three categories, based on clinical significance, category A (Immediate clinical relevance), category B (findings considered indeterminate but most likely benign) and category C (incidental findings of no clinical significance).

Statistical analysis

Statistical analysis was done using the SPSS statistical software (SPSS, version 18.0 for Windows; SPSS Inc., Chicago, IL, United States). Discrete and continuous variables are presented as counts and percentages, and as mean ± SD respectively. Non-normal variables were expressed as medians and interquartile ranges (25^{th} and 75^{th} percentiles).

RESULTS

A total of seventy nine cases (79/1343, 5.8%) of peripheral CTAs imaged the upper limbs and were subsequently analyzed. From these studies, four patients were excluded as a result of incomplete imaging datasets. Of the 74 patients (52.7% females, 47.3% males) with complete upper limb CTA imaging, the mean age was 59 59 ± 19.5 years (range 19-93 years).

One hundred fifty-three EVIFs were identified in 52 patients (70.3%). 44 EVIFs

(28.7%) were noted in the chest, 83 (54.2%) were found in the abdomen, 14 (9.2%) in the musculoskeletal system and 9 (5.8%) in the head and neck.

Thirteen (8.4%) EVIFs were identified in 11 patients and were considered of immediate clinical significance (category A), demonstrated in Table 1. The majority of category A findings were noted in the chest (n = 8), with additional highly significant findings (all cases were of ascites) noted in the abdomen/pelvis (n = 3) with sclerotic bone lesions (n = 1) and osteomyelitis (n = 1) identified on examination of the musculoskeletal system.

Six category A EVIFs were concerning for a new malignancy diagnosis (n = 1) or disease progression (n = 4) or recurrence (n = 1). Details regarding further investigation and follow-up are outlined in Table 2. One male patient, symptomatic with acute upper limb ischaemia was found to have an irregular 16mm nodule in the right upper lobe with ipsilateral hilar lymphadenopathy on CT. Subsequent CT-guided biopsy confirmed histopathological diagnosis of lung adenocarcinoma.

Three patients demonstrated new progression of existing malignancy on upper limb CTA, one case of cholangiocarcinoma with new pulmonary and osseous metastases and two patients with prostate cancer and new pulmonary metastasis. Breast cancer recurrence, confirmed on CT-guided mediastinal lymph node biopsy in a patient with new chest lymphadenopathy, was also diagnosed on upper limb CTA.

A single patient with a history of prior breast cancer was found to have a new spiculated breast nodule identified on upper limb CTA but did not have follow-up imaging available at our institution.

Fifty EVIFs (32.3%) were identified in 20 patients and were considered indeterminate but most likely benign (category B) and are demonstrated in Table 3.

The majority of EVIFs were of no clinical significance (n = 21, 59.5%) and placed in category C (Table 4). The most common category C finding was simple renal cysts (n = 12).

DISCUSSION

CTA has become the principal investigation when assessing vascular patients and with the added capability of imaging extravascular structures, it offers the opportunity to discover incidental findings unrelated to the study indication. Such incidental findings can subsequently lead to the diagnosis of a life-threatening condition and can be of paramount importance in these groups of patients.

In 13 (8.4%) patients, the EVIF were identified as requiring immediate follow-up with further diagnostic tests. This is of particular importance in cases of new cancer diagnosis or progression of malignancy as survival rates may decrease significantly the earlier the cancer is identified and treated.

The results of our study compare similarly with prior studies looking at EVIF with regards to the frequency of detecting new (1.3%) or progression of pre-existing malignancy (5%). Naidu *et al*[6] described 40 highly significant EVIFs of which nine (3%) were confirmed malignancies. Iezzi *et al*[5] noted 15 index cancer cases (3.5%) in their series while Preuß *et al*[7] identified 4 malignancies (2.8%). The most common solid malignancies identified in all studies were pulmonary neoplasms. Belgrano *et al*. identified 36 solid masses of possible malignant nature (4.5%) but did not provide follow-up or correlation with histopathology [11]. Of note, and similarly to the studies by Naidu *et al*[6] and Preuß *et al*[7], we correlated the EVIFs identified in our patient cohort with the patient's clinical background, including any past history of malignancy.

Our sample size was smaller (n = 79) in comparison with prior reports regarding the frequency and clinical relevance of EVIFs on CTA studies, with patient cohorts ranging from 141[7] to 821[12], despite the fact that our retrospective study was performed over a similar time-period (24 mo) to previous articles pertaining to this topic. We can potentially account for this by recognizing that CTA of the upper limb is a relatively infrequently performed examination in comparison with arterial CT imaging of the lower limbs, the latter performed far more consistently and for a wider variety of indications.

Furthermore, the mean age of patients in our study was 59 years old, a much younger demographic in comparison to prior studies examining for EVIF on CTA exams[5-7,12]. For example, the mean age of patients in the study by Preuß *et al*[7] was 80 years old. The younger mean age in our report can be accounted for by the fact that our study demonstrated a much broader range of patient ages (18-90 years old), the median age was 67 years old, which was similar to the median age of previous studies.

To the best of our knowledge, this study is the first to evaluate for the presence of

Table 1 A total of 13 category A extravascular incidental findings (immediate clinical significance) were identified

Region	EVIF	Number of cases
Chest	Lung nodule > 1 cm	4
	Breast nodule	1
	Mediastinal lymphadenopathy	1
	Oesophageal wall thickening	1
	Pleural effusion	1
Abdomen/pelvis	Ascites	3

EVIF: Extravascular incidental finding.

head and neck extravascular incidental findings on CTA of the upper limb. Nine EVIF were present in the head and neck, however, no Category A EVIFs were identified.

Our work shows the importance of detecting EVIFs. The early detection of cancer can be significant for patient outcomes and can ultimately reduce health costs by offering a curative surgical option. This may therefore, justify reporting and following up on incidental findings. However, a cost-effective analysis of pursuing incidental findings in addition to long term studies comparing CTAs in vascular patients who did not have their extravascular findings reported needs to be conducted to adequately understand the true value of EVIFs. Attempts to provide guidance on the management of incidental findings have been made[13] however data on cost-effectiveness is sparse.

Limitations

As a retrospective study, the correlation of clinical symptoms with radiological findings was not performed for all EVIFs. In our study, follow-up data was available in 5/13 (38.5%) of Category A EVIFs, all of which pertained to suspected primary malignancy or progression of disease. This was a limitation noted in past studies[5-9] of a similar nature where there was a lack of follow up imaging. For example, in the study by Naidu *et al*[6], 42% of patients did not have follow-up imaging. Secondly, the use of arterial phase imaging in the examination of the abdominal and pelvic viscera can limit evaluation of hypovascular lesions and pathology more reliably detected on portal venous or delayed phase studies. Thirdly, unilateral imaging was performed in all 79 patients, of either the left or right arm, or hemithorax, therefore potentially reducing the number of EVIFs identified in each patient.

We propose a new emailing alert system in which the radiologist reporting the scan flags up any significant EVIF which would send an automated email to both the referrer and the consultant the patient is under. In addition, a clinical nurse specialist has been allocated the responsibility of ensuring these are correctly followed up. This minimises the risk of losing patients to follow-up and we recommend a similar system is put into place across all hospitals.

Conclusion

In conclusion, our work signifies the importance of reporting both vascular and extravascular findings in CTAs, especially in this patient group of higher risk. Incidental findings are very common, and although most are of a benign nature, they do lead to the detection of serious life-threatening pathology which would otherwise be missed or diagnosed late. Although arterial phase CT imaging of the upper limb is a less commonly requested and performed peripheral arterial examination, both referring physicians and interpreting radiologists must recognize the frequency and relevance of incidental findings in this patient cohort allowing timely and appropriate clinical and imaging follow up.

Table 2 Details of the follow-up for the six patients with suspicious incidental findings

Incidental finding	Follow-up imaging study	Diagnosis
Multiple pulmonary nodules and sclerotic bone lesions	Plain film radiography of hip, femur, knee, CT TAP (staging)	Metastatic cholangiocarcinoma (new lung and bone lesions)
Pulmonary nodule (> 1 cm) with hilar lymph node enlargement	CT TAP (staging)	Lung adenocarcinoma (index diagnosis)
Mediastinal lymphadenopathy (prior breast cancer)	CT TAP (staging), CT-guided lymph node biopsy	Metastatic breast cancer (recurrence of primary cancer)
Breast nodule (prior breast cancer)	Breast ultrasound (recommended)	Follow up imaging unavailable
Multiple lung nodules	CT TAP (staging)	Metastatic prostate cancer (new lung lesions)
Lung nodule	CT TAP (staging)	Metastatic prostate cancer (new lung lesions)

CT: Computer tomography.

Table 3 Category B lesions (indeterminate but most likely benign) accounted for 50 extravascular incidental findings

Region	EVIF	Number of cases
Chest	Lung nodule (> 4, < 10 mm)	2
	Lung lobar atelectasis	1
	Pleural thickening	1
Abdomen/pelvis	Prominent lymph nodes (≤ 1 cm)	13
	Hiatal hernia	5
	Enlarged prostate gland	3
	Adrenal hyperplasia	2
	Renal infarct	1
	Urinary bladder wall thickening	1
	CBD dilatation	1
	Gallbladder distension	1
	Intrahepatic biliary duct dilatation	1
	Prostatic calcification	1
	Inguinal hernia	1
Musculoskeletal	Sclerotic bone lesions	5
	Pectoralis major atrophy	1
	Spinal stenosis	1
	Spondylolisthesis	1
	Spinal scoliosis	1
Head/neck	Thyroid nodule	1
	Prominent lymph nodes (≤ 1 cm)	6

EVIF: Extravascular incidental findings.

Table 4 Category C abnormalities (lesions of no clinical significance) accounted for 91 extravascular incidental findings

Region	EVIF	Number of cases
Chest	Interstitial lung disease	11
	Emphysema	8
	Pulmonary consolidation	5
	Pleural calcification	3
	Pneumatocele	3
	Bronchiectasis	1
	Pulmonary nodule < 4 mm	1
Abdomen/pelvis	Renal cyst	12
	Diverticular disease	10
	Cholecystolithiasis	6

	Atrophic kidney	5
	Focal liver fat sparing	4
	Hepatic cyst	4
	Fatty infiltration of the liver	3
	Adrenal lipoma	2
	Atrophic pancreas	1
	Calcified uterine fibroid	1
	Omental fat stranding	1
	Renal scar	1
	Splenic cyst	1
	Scrotal hydrocele	1
	Groin sinus tract	1
Musculoskeletal	Clavicle fracture (old)	1
	Pelvic fracture (old)	1
	Humeral head fracture (old)	1
	Generalised osteopenia (humeral head)	1
Head/neck	Thyroid goitre	1
	Paranasal sinus mucocele	1

EVIF: Extravascular incidental finding.

ARTICLE HIGHLIGHTS

Research background

Recent developments and improvements in image acquisition and spatial resolution with multi-detector computed tomography has resulted in computed tomographic angiography (CTA) to become the first line-line investigation for upper limb pathology, replacing the more invasive digital subtraction angiography. It has the added capability of imaging the surrounding extravascular anatomy leading to the detection of incidental mass/lesions. The significance of these "incidental" findings has mixed opinions. Whilst evidence has shown them to identify potentially life-threatening pathologies, they can also lead to an unnecessary diagnostic cascade of investigations only for the end result to be benign. We set out to report the frequency and more importantly the clinical relevance of these incidental findings to better understand their significance.

Research motivation

We set out to establish the frequency of incidental findings and to follow-up to determine their end significance in upper limb CTA. This has yet to be been described in the literature. Incidental findings can lead to an unnecessary investigation cascade and therefore we wanted to determine the proportion of incidental findings which do lead to the diagnosis of a life-threatening pathology. This will raise awareness in the medical field of the importance for both the reporting radiologist and the referring physician of the need to recognise these findings and arrange appropriate follow-up. Evidence has shown cancer pathology is picked up through their detection and therefore highlights the importance of the reporting radiologist spending extra time to report structures outside of the scan indication.

Research objectives

Our objective was to report the frequency of incidental findings in CTA of the upper limb over a 2 year period. Those with findings of significance were followed up to determine their clinical outcome. We found incidental findings in over two thirds of patients, with 8.4% of them being of immediate clinical significance and detecting one index case of malignancy and four cases of new disseminated metastatic disease. Spending extra time reporting masses/lesions outside of the intended anatomy can significantly improve patient outcomes.

Research methods

Consecutive upper limb CTAs performed at Guys and St Thomas hospitals between August 2015 to August 2017 were retrospectively reviewed for inclusion. Patient demographics, incidental findings and their follow-up were entered into an excel spreadsheet and statistical analysis was done using SPSS statistical software (SPSS, version 18.0 for Windows; SPSS Inc., Chicago, IL, United States). Incidental findings were grouped into category A (immediate), category B (indeterminate) or category C (no clinical significance). Conversely to other work in the literature, we retrospectively reviewed CTA reports rather than re-reviewing CTA images for incidental findings. This was to better reflect the current clinical practice as re-evaluation of images for incidental findings would theoretically increase their detection. Prior imaging studies were used as the standard of reference. Those with suspicious findings were followed to determine their significance.

Research results

A total of 153 extravascular incidental findings (EVIFs) were reported in 52 patients. Of these 13 EVIFs (8.4%) were Category A, 50 EVIFs (32.3%) were Category B, while 91 EVIFs (59.5%) were Category C. One index case of malignancy (1.3%) and four cases of new disseminated metastatic disease (5.4%) were identified. This is the first study to describe incidental findings in CTAs of the upper limbs. Detecting incidental findings can be of paramount importance however a large proportion also end of being benign. More work is needed in the recommendation of their follow-up and on cost-effective.

Research conclusion

The purpose of this study was to report the frequency and more importantly the clinical relevance of extravascular lesions in patients undergoing upper limb CTA, including the frequency of index cases and progression of known cancer cases. We identified one index case of malignancy, and four cases of new disseminated metastatic disease. Our work shows the importance of detecting EVIFs. The early detection of cancer can be significant for patient outcomes and can ultimately reduce health costs by offering a curative surgical option. This may therefore, justify reporting and following up on incidental findings. To the best of our knowledge, this study is the first to evaluate for the presence of head and neck extravascular incidental findings on CTA of the upper limb. Nine EVIF were present in the head and neck, however, no category A EVIFs was identified. Although arterial phase CT imaging of the upper limb is a less commonly requested and performed peripheral arterial examination, both referring physicians and interpreting radiologists must recognize the frequency and relevance of incidental findings in this patient cohort allowing timely and appropriate clinical and imaging follow up. However, a cost-effective analysis of pursuing incidental findings in addition to long term studies comparing CTAs in vascular patients who did not have their extravascular findings reported needs to be conducted to adequately understand the true value of EVIFs. Attempts to provide guidance on the management of incidental findings have been made however data on cost-effectiveness is sparse.

Research perspectives

Incidental findings are very common, and although most are of a benign nature, they do lead to the detection of serious life-threatening pathology which would otherwise be missed or diagnosed late. It is important for the reporting radiologist to be aware of their frequency to lead to their detection. More work is needed on guidelines for their management to aid in appropriate follow-up and to avoid an unnecessary cascade of investigations. Future work on their cost-effectives is needed and clinical outcomes to quantitively measure their importance. This can be completed in a long-term CTA study to assess if earlier detection of malignancy improves patient survival rates.

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