82062_Auto_Edited.docx

WORD COUNT 3929
TIME SUBMITTED 04-JAN-2023 08:38PM
PAPER ID 95181174

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 82062

Manuscript Type: ORIGINAL ARTICLE

Retrospective Study

COVID-19 Related Myocardiopathy: Can Dual- Energy Computed Tomography Be a Diagnostic Tool?

Can COVID-19 Related Myocardiopathy Be Diagnosed With DECT?

Fahri Aydin, Mecit Kantarci, Sonay Aydın, Erdal Karavaş, Gökhan Ceyhun, Hayri Ogul, Cagri Emin Sahin, Suat Eren

Abstract

BACKGROUND

No study on DECT has been found in the literature to evaluate possibly fatal cardiac/myocardial problems in COVID-19 patients. Myocardial perfusion deficits can be found in COVID-19 patients even without any significant coronary artery occlusion and these deficits can be shown *via* DECT with a perfect interrater agreement

AIM

Recently, Dual- Energy Computed Tomography (DECT) perfusion imaging was used to assess lung perfusion alterations in COVID-19. To our knowledge, no study on DECT has been found in the literature to evaluate possibly fatal cardiac/myocardial problems in COVID-19 patients. The purpose of this study is to evaluate the role of DECT in the detection of COVID-19-related cardiac diseases.

METHODS

Two blinded independently examined the CT images using the 17-segment model according to the American Heart Association classification of the segmentation of the left ventricular myocardium. Additionally, intraluminal diseases and abnormalities in the main coronary arteries and branches were investigated. Following segment-by-segment analysis, the perfusion deficiencies on the iodine map pictures on DECT were identified.

RESULTS

The study enrolled a total of 87 patients. 42 of these individuals were classified as COVID-19 positive cases, while 45 were classified as controls. Perfusion deficit was identified in 66.6% (n = 30) of the cases. All control patients had a normal iodine distribution map. Perfusion deficits were found on DECT iodine map images with a subepicardial (n = 12, 40%), intramyocardial (n = 8, 26.6%), or transmural (n = 10, 33.3%)

anatomical location within the left ventricular wall. There was no subendocardial involvement in any of the patients.

CONCLUSION

Myocardial perfusion deficits can be found in COVID-19 patients even without any significant coronary artery occlusion. These deficits can be shown *via* DECT with a perfect interrater agreement. Perfusion deficit presence is positively correlated with D-dimer levels.

Key Words: DECT; COVID-19; Heart; Perfusion; D-dimer

Aydin F, Kantarci M, Aydın S, Karavaş E, Ceyhun G, Ogul H, Sahin CE, Eren S. COVID-19 Related Myocardiopathy: Can Dual- Energy Computed Tomography Be a Diagnostic Tool? *World J Clin Cases* 2022; In press

Core Tip: To our knowledge, there hasn't been any research on Dual- Energy Computed Tomography (DECT) done to assess potentially fatal cardiac/myocardial issues in COVID-19 patients. This investigation's goal is to assess DECT's contribution to the identification of cardiac conditions associated with COVID-19. the result Even in COVID-19 patients without any significant coronary artery occlusion, myocardial perfusion deficits can be identified, and these deficits can be demonstrated *via* DECT with perfect inter-observer agreement.

INTRODUCTION

COVID-19 is an infectious disease that first surfaced in China in December 2019 and quickly spread throughout the world. The SARS-CoV-2 virus, which is the disease's causal agent, causes a clinical picture that largely affects the respiratory system (1). The Angiotensin-Converting Enzyme II (ACE2) protein is found in the respiratory system, intestinal enterocyte cells, cardiac muscle cells, and vascular endothelial cells and is

thought to be exploited by SARS-CoV-2 for cell entrance. The SARS-CoV-2 virus is hypothesized to start the inflammatory response by inhibiting ACE2. Thus, systemic cytokine release is said to start, which can induce not just lung injury but also systemic harm such as multiorgan dysfunction. With procoagulant action, systemic inflammation sensitizes vascular plaques and raises the risk of cardiovascular disease (2).

Several different theories were suggested to explain the pathophysiology of COVID-19 disease cardiac involvement. The pathophysiological processes uncovered are demonstrated as potential sources of cardiac damage in COVID-19 patients, and this myocardial damage manifests itself in various clinical images. Among the most commonly documented cardiac problems in COVID-19 patients are acute myocarditis, acute myocardial infarction, arrhythmias, cardiomyopathies, and acute heart failure. All of these cardiovascular problems significantly increase morbidity and mortality in COVID-19 patients. As a result, early detection and treatment of these consequences is critical (3, 4).

Previous research has mostly focused on the significance of cardiac magnetic resonance (CMR) imaging in COVID-19 patients. CMR has been demonstrated to be useful in determining the mechanism, prevalence, and amount of myocardial damage. Myocarditis is the most prevalent imaging diagnostic, with mapping anomalies and myocardial edema on T2 being the most common imaging findings, followed by LGE. Furthermore, in a study of individuals who had recently recovered from COVID-19 infection, CMR revealed cardiac involvement and myocardial inflammation without considering previous comorbidities, the severity and overall course of the acute illness, or the time from the original diagnosis (5, 6). Despite the fact that CMR was found to be effective in detecting COVID-19-related myocardial problems, it has some drawbacks, including a long scan time, the fact that it is not universally available, the high cost, claustrophobia, incompatibility with pacemakers, and incompatibility with prostheses (7, 8).

Dual- Energy Computed Tomography (DECT) is a developing technology that provides information about the material composition *via* image acquisition by varying photon

energy levels (9). In the last decade, DECT has been increasingly utilized for cardiac imaging (10, 11). When different energy levels of X-ray spectra are penetrated through iodine-based contrast medium, and reveals unique absorption characteristics. As a result, iodine mapping reveals the distribution of iodine in the myocardium (10), where the dark areas indicate a lack of iodine DECT detects cardiac perfusion defects very precisely (12, 13).

Recently, DECT perfusion imaging was used to assess lung perfusion alterations in COVID-19 (14, 15). To our knowledge, no study on DECT has been found in the literature to evaluate possibly fatal cardiac/myocardial problems in COVID-19 patients. The aim of the current study is to assess the role of DECT in the detection of COVID-19-related cardiac diseases.

MATERIALS AND METHODS

The local institutional review board approved this study, and as a result of retrospective nature, informed consent was waived.

Patients:

Data from this retrospective study include patients from January 2021 to June 2022.Case group included hospitalized individuals with the diagnosis of COVID-19 who had a cardiology consultation due to chest pain and underwent DECT on suspicion of heart abnormalities. COVID-19 was identified using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests on nasal and pharyngeal swabs.

As a control group, we included patients who had a DECT scan to evaluate chest pain and a negative RT-PCR assay of nasal and pharyngeal swabs for COVID-19. For both study and control groups,; an exclusion criterion was the existence of any previously known concomitant condition (coronary artery disease, hypertension, hyperlipidemia, diabetes, history of coronary stent or by-pass, arrhythmia, *etc.*). Furthermore, etiological factors that may induce D-dimer increase, such as deep venous thrombosis, pulmonary embolism, liver and renal failure, were evaluated, and patients with these conditions

were eliminated. Finally, DECT examinations with insufficient qualifications (with poor image quality and numerous artifacts) were barred.

A five-point scale was utilized to evaluate the image quality of each coronary segment on DECT: There are no motion artefacts in 5, minor artefacts (mild blurring) in 4, moderate artefacts (moderate blurring without discontinuity) in 3, severe artefacts (doubling or discontinuity along the coronary segments) in 2, and unreadable artefacts (doubling or discontinuity along the coronary segments) in 1 (vessel structures not differentiable). A score of 4 was deemed good for image quality.

49 patients met the inclusion criteria, however 7 were omitted (insufficient image quality in 3 patients, history of diabetes in 1 patient, presence of a previously applied coronary stent in 1 patient, and presence of deep venous thrombosis in 2 patient). 42 patients were included.

DECT protocol:

The DECT images were created *via* a 64-slice dual-source multi-detector CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). 1 mL/kg body weight iopromide (Ultravist 370 mg/mL, Bayer Schering Pharma, Berlin, Germany) was administered into the right antecubital vein with a flow rate of 5 mL/s, followed by 60 mL saline. A bolus tracking technique was used to pinpoint the area of interest (ROI) in the left ventricle (CARE-bolus, Siemens Healthcare, Forchheim, Germany). The data collection procedure was initiated at a predetermined time interval specified by a single ROI system with a trigger threshold of 200 HU in the left ventricular blood pool. Data collection commenced eight seconds after triggering, with arterial phase data being gathered. Retrospective ECG pulsing with low-pitch ECG-gated scan was used as the scan mode (a prospective protocol could not be applied due to the artifacts during the dual-energy protocol). All patients in the retrospective procedure received ECG dosage modulation. The CT dose index volume and the dosage-length product of all the scans were recorded.

Patients were encouraged to adopt the deep-inspiration breath-hold technique during the procedure, and the scan was conducted craniocaudally from the subcarinal level to the diaphragm. The reconstruction window of the initial axial pictures was set at 75% (end of diastolic phase) and 45 percent for the cardiac cycle (end of systolic phase).

For the myocardial evaluation, the high (140 kV)- and low-voltage (80 kV) information were reconstructed *via* a dual-energy convolution core (D30f) that has a temporal resolution of 140 milliseconds and a thickness of 1.5 mm, with 1 mm increments utilized to maximize the signal-noise ratio. Following that, the final data was analyzed using a three-material decomposition software platform (Syngo Multimodality Workplace; Siemens, Erlangen, Germany).

Image analysis:

Two blinded radiologists (18 and 6 years of experience in cardiac CT) independently examined the CT images using the 17-segment model according to the American Heart Association classification of the segmentation of the left ventricular myocardium. If the two independent readers disagreed on AE diagnosis, a consensus reading was performed. Additionally, intraluminal diseases and abnormalities in the main coronary arteries and branches were investigated. Prior to analyzing the myocardium with DECT, the 'DE normalize contrast' process was used on the workstation to provide consistency for the visual evaluation and eliminate any bias due to inter-observer variability. Myocardial assessment was performed using arterial phase pictures. The dark spots on the color-coded iodine map were identified as perfusion deficiencies for each subject and section.

Following segment-by-segment analysis, the perfusion deficiencies on the iodine map pictures on DECT were identified. Each segment was also counted in terms of the number of segments involved and its anatomic location (transmural, intramyocardial, subepicardial, subendocardial).

Statistical analysis:

SPSS version 20.0 was utilized (SPSS Inc, Chicago, IL, USA). To evaluate the normally distributed data, the Kolmogorov-Smirnov test was utilized. Numerical variables with a

normal distribution were expressed as mean± standard deviation (SD), but those with an atypical distribution were expressed as median (minimum-maximum) values. Number (n) and percentage values were used to denote categorical variables (%). On DECT scan, patients were classified according to the presence or absence of coronary artery stenosis and myocardial perfusion deficit. The Mann-Whitney U test for age distribution and the Chi-square test for gender and percentage distribution were used to determine compatibility in both groups. The influence of D-dimer on predicting the presence of perfusion deficit was described using logistic regression analysis. The correlation between HU and D-dimer values was tested with Pearson's correlation. Observers 1 and 2 independently assessed the CT images for the presence of perfusion deficits. Cohen's Kappa coefficient was used to determine whether Observer 1 and Observer 2 were in agreement. Accordingly, the degree of agreement was classified as slight if the coefficient was between 0 and 0.20, fair if the coefficient was between 0.21 and 0.40, moderate if the coefficient was between 0.41 and 0.60, substantial if the coefficient was between 0.61 and 0.80, and almost perfect if the coefficient was between 0.81 and 1.00 (16). A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The current study enrolled a total of 87 patients. 42 of these individuals were COVID-19 positive cases, while 45 were classified as negative controls. Tables 1 shows the age, troponin-I, and D-dimer distributions of the patients.

In the case group, mild coronary artery stenosis was detected in 9.5% (n = 4) of patients while significant stenosis (any stenosis larger than or equal to 50% was considered significant) was detected in 4.7% (n = 2) of patients. In the control group, 11.1 % (n = 5) of patients had mild coronary artery stenosis. The prevalence of mild or significant coronary artery stenosis was comparable between the study and control groups ($p>0.05$). Additionally, no structural changes or myocardial bridging were found in eighter study or control group.

Perfusion deficit was identified in 66.6% (n = 30) of the case group in the myocardial perfusion imaging data analyzed with the iodine distribution map. On the other hand no perfusion deficit was detected in the control group (Figure 1). Rate of presence of myocardial perfusion deficits was significantly higher in the case group ($p<0.001$).

Perfusion deficits were found on DECT iodine map images with a subepicardial (n = 12, 40%), intramyocardial (n = 8, 26.6%), or transmural (n = 10, 33.3%) anatomical location within the left ventricular wall (Figure 2-4). There was no subendocardial involvement in any of the patients. Involvement patterns did not correspond to any coronary artery territories. ROI was used to measure the perfusion deficit and normal areas on the iodine map images on DECT. The mean value of the normal areas was 132.437 ± 31.11 HU (range, 60-217), while that of the perfusion deficits was 51.25 ± 17.19 HU (range, 28-86). Troponin-I levels had no significant connection with HU values in perfusion deficit areas ($p>0.05$). The HU levels of the perfusion deficits, on the other hand, increased in tandem with the D-dimer values (r = 0.765, P = 0.01).

In the case group, there was no significant connection between troponin-I elevation and the occurrence of a myocardial perfusion deficit ($p> 0.05$). In this group, there was a significant connection between D-dimer increase and the occurrence of a perfusion deficit (higher d-dimer levels correlate with higher number of involved segments with perfusion deficit) (P = 0.012). Furthermore, it was discovered in the case group that an increase in D-dimer levels (upper limit of normal 500 ng/mL) increased the likelihood of the occurrence of perfusion deficits thrice (OR:3, $p<0.001$, CI 95%: 1.47-6.14).

Between Observer 1 and Observer 2, there was a substantial consistency in the existence of myocardial perfusion deficit across the entire study group. There was perfect agreement between the two observers ($p<0.001$, kappa value=0.896).

DISCUSSION

Using the dual-source CT angiography approach, we compared the COVID-19 positive group to the control patient with clinical suspicion of coronary arterial disease. We did not find any significant difference in coronary luminal abnormalities between the

groups. However, myocardial perfusion abnormalities were substantially more common in the COVID-19 case group compared to the controls. Furthermore, both observers revealed perfusion deficiencies with perfect agreement. These perfusion deficit locations were deemed to be substantial in terms of myocardial damage, correlating to the dark lesions in the iodine mapping method.

ACE2 is the host cell receptor for the SARS-CoV-2 spike protein, that *via* itself, the virus can infect the heart, vascular tissues, and circulating cells. One of the frequent extrapulmonary signs of COVID-19 is acute cardiac injury which can have long-term consequences. ACE2 can be detected in various tissues, such as the heart, lung, intestines, kidney, testis, nose, and mouth. Nasal and pulmonary epithelial cells are accepted to be the primary sites of the infection, however following initial viral replication, myocardial cells can also exhibit necessary components for viral uptake. According to gene expression investigations, the ventricular myocardium possesses all of the essential mediators of SARS-CoV-2 binding and entrance (17, 18).

Evidence of acute cardiac compromise is not rare in hospitalized COVID-19 patients, including acute heart failure (3%–33%), cardiogenic shock (9%–17%),myocardial ischemia or infarction (0.9%–11%),left ventricular dysfunction (10%–41%), right ventricular dysfunction (33%–47%), biventricular dysfunction (3%–15%), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%), and arterial thrombosis secondary to viral-mediated coagulopathy (19). It was discovered that D-dimer and fibrinogen degradation products can be raised in COVID-19 cases as a result of viral-mediated coagulopathy and microangiopathy. Additionally, D-dimer values were shown to be related with the presence and extent of lung perfusion anomalies discovered using DECT (14, 15), as well as the presence of long COVID symptoms (20).

CMR abnormalities suggestive of damage were previously often recorded. CMR findings such as T1 mapping pathologies (which may indicate extensive myocardial damage like fibrosis and/or edema); T2, short tau inversion recovery, or T2 mapping abnormalities (more specific findings of myocardial inflammation, similarly with acute

myocarditis); late gadolinium enhancement (LGE, as a sign of acute myocardial injury and/or fibrosis); or pericardial involvement. All of these findings can be accepted as cardiac COVID-19 associated problems (19, 21).

While CMR manifestations of cardiac COVID-19 have been extensively explored, there is no study to our knowledge that describes myocardial perfusion anomalies through DECT. We have demonstrated that DECT can accurately detect COVID-19-related cardiac perfusion abnormalities. Additionally, we reduced the effect of false positive results produced by ischemia episodes by utilizing a control group. We were unable to pinpoint the perfusion deficits to a vascular territory and did not discover any perfusion deficit in the subendocardial area when segmental and regional distributions were evaluated. Additionally, these data rule out the notion that the perfusion deficiencies were caused primarily by coronary artery obstruction and ischemia, rather than by COVID-19-associated myocardiopathy. Moreover, these findings support the hypothesis of direct viral myocardial damage.

According to our findings, even in the absence of severe coronary artery obstruction, COVID-19 patients' myocardium exhibits perfusion abnormalities. Additionally, we demonstrated a favorable correlation between high D dimer values and perfusion impairments. These findings are consistent with the previously defined fact that COVID-19 induces microangiopathy and that D-dimer levels serve as a marker for the microangiopathic process. As with lung perfusion deficits discovered using DECT, increased D dimer values are associated with myocardial perfusion problems, which can be diagnosed with cardiac DECT.

Troponin levels are elevated in 20% to 30% of hospitalized individuals with COVID-19. According to these elevated troponin levels, acute myocardial injury occurs at an overall incidence of between 8% and 62%, with a higher prevalence of elevated troponin levels being associated with worse disease severity (22, 23). On the other hand, despite abnormal CMRs, three trials revealed normal troponin levels following COVID-19 (23-25). We could not detect any relation between troponin-I levels and cardiac perfusion

deficits. This result might be explained with the phase or the severity of the myocardiopathy.

In cases of COVID-19, chest pain and thromboembolic cardiovascular complications are extremely common. Particularly in emergency situations, chest pain caused by COVID-19 pneumonia and other cardiovascular complications or diseases can easily coexist. Cardiac CT exams are increasingly utilized in the diagnostic evaluation of chest pain (14). By using DECT to detect COVID-19-associated myocardial damage and distinguish this entity from other cardiovascular causes in a single session, we can provide rapid and effective diagnosis and treatment. In addition, CMR, the alternative diagnostic tool for defining COVID-19-associated myocardial damage, is more difficult to access and considerably more costly than DECT. In addition to more claustrophobic complaints, CMR has longer examination periods, too (26). There are a few significant limitations in this study. The study's retrospective nature and small sample size are the key restrictions. Coronary arterial findings were not confirmed invasive angiography. CMR scans were not done on any of the individuals included in the study to confirm the identified perfusion anomalies. We are unable to offer patients with clinical follow-up data.

CONCLUSION

To conclude, myocardial perfusion deficits can be found in COVID-19 patients even without any significant coronary artery occlusion. These deficits can be shown *via* DECT with a perfect interrater agreement. Perfusion deficit presence is positively correlated with D-dimer levels.

ARTICLE HIGHLIGHTS

Research background

Previous research has mostly focused on the importance of cardiac magnetic resonance (CMR) imaging in COVID-19 patients. Although CMR has been found to be effective in detecting myocardial problems associated with COVID-19, Dual Energy Computed

Tomography (DECT) is increasingly used for cardiac imaging due to its long scanning time, non-universal and high cost.

Research motivation

To the best of our knowledge, there has been no study in the literature on DECT evaluating potentially fatal cardiac/myocardial problems in patients with COVID-19. The aim of the current study is to evaluate the role of DECT in detecting COVID-19-related heart disease.

Research objectives

In COVID-19 patients without significant coronary artery occlusion, myocardial perfusion deficits can be demonstrated by DECT.

Research methods

Data from this retrospective study include patients between January 2021 and June 2022. The case group includes individuals hospitalized with a diagnosis of COVID-19 who had a cardiology consultation due to chest pain and underwent DECT for suspected heart abnormality. DECT images were generated as follows: 64-slice dual-source multidetector CT scanner 1 mL/kg body weight iopromide was applied. Two blind radiologists independently reviewed CT images using the 17-segment model according to the American Heart Association classification.

Research results

A total of 87 patients were included in the current study. Of these people, 42 were COVID-19 positive cases, while 45 were classified as negative controls. No perfusion deficit was detected in the control group. The presence of myocardial perfusion deficit was significantly higher in the case group ($p<0.001$). Involvement patterns did not correspond to any coronary artery region. HU levels of perfusion deficits increased in parallel with D-dimer values ($r = 0.765$, $P = 0.01$). There was a significant correlation

between the increase in D-dimer and the formation of perfusion deficit in the case group (P = 0.012). Moreover, it was discovered that the increase in D-dimer levels (upper limit of normal 500 ng/mL) in the case group increased the probability of perfusion deficit to occur threefold (OR:3, p<0.001, CI 95%: 1.47-6.14). There was excellent agreement between observers (p<0.001, kappa value=0.896).

Research conclusions

ACE2 is the host cell receptor for the SARS-CoV-2 spike protein, and the virus can infect the heart, vascular tissues, and circulating cells on its own. One of the common extrapulmonary manifestations of COVID-19 is acute cardiac injury, which can have long-term consequences.

According to gene expression investigations, the ventricular myocardium possesses all of the essential mediators of SARS-CoV-2 binding and entrance.

It was discovered that D-dimer and fibrinogen degradation products may be elevated in COVID-19 cases as a result of viral-mediated coagulopathy and microangiopathy. In addition, D-dimer values have been shown to correlate with the presence and extent of lung perfusion abnormalities discovered using DECT and the presence of prolonged COVID symptoms.

Abnormalities suggestive of cardiac magnetic resonance injury have been frequently noted before. A study describing myocardial perfusion anomalies with DECT is not within our knowledge. We demonstrated that DECT can accurately detect cardiac perfusion abnormalities associated with COVID-19.

In addition, we demonstrated a positive correlation between high D dimer values and perfusion disorders. Troponin levels are elevated in 20% to 30% of individuals hospitalized with COVID-19. We could not detect any relationship between troponin-I levels and cardiac perfusion deficits.

We have shown that in can accurately detect cardiac perfusion abnormalities associated with COVID-19.

In addition, we demonstrated a positive correlation between high D dimer values and perfusion disorders. Troponin levels are elevated in 20% to 30% of individuals hospitalized with COVID-19. We could not detect any relationship between troponin-I levels and cardiac perfusion deficits.

We have shown that in can accurately detect cardiac perfusion abnormalities associated with COVID-19.

Research perspectives

As a result, myocardial perfusion defects may be present in patients with COVID-19 even without significant coronary artery occlusion. These defects can be demonstrated *via* DECT with excellent interoperator compatibility. Presence of lack of perfusion is positively correlated with D-dimer levels.

82062_Auto_Edited.docx

ORIGINALITY REPORT

8%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.dirjournal.org Internet	112 words — 3%
2	www.ncbi.nlm.nih.gov Internet	75 words — 2%
3	tmg.org.rs Internet	45 words — 1%
4	Mina K. Chung, David A. Zidar, Michael R. Bristow, Scott J. Cameron et al. "COVID-19 and Cardiovascular Disease", Circulation Research, 2021 Crossref	16 words — < 1%
5	f6publishing.blob.core.windows.net Internet	16 words — < 1%
6	www.nature.com Internet	15 words — < 1%
7	bmcmusculoskeletdisord.biomedcentral.com Internet	13 words — < 1%
8	"中華核医学と分子イメージング雑誌 Volume 38, Number 10, October 25, 2018", 核医学, 2018 Publications	12 words — < 1%

9	Fabiola B. Sozzi, Elisa Gherbesi, Andrea Faggiano, Eleonora Gnan et al. "Viral Myocarditis: Classification, Diagnosis, and Clinical Implications", Frontiers in Cardiovascular Medicine, 2022 Crossref	12 words — < 1%
10	acamedicine.org Internet	12 words — < 1%
11	mdpi-res.com Internet	12 words — < 1%
12	opencommons.uconn.edu Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	OFF	EXCLUDE MATCHES	< 12 WORDS