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RESEARCH ARTICLE

## Negative impact of prolonged fasting on gallbladder ejection fraction measurement with cholescintigraphy in Chronic Acalculous Symptomatic hyperkinetic (CASPER) gallbladders

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### ABSTRACT

*Background:* Chronic Acalculous Symptomatic hyperkinetic (CASPER) gallbladder is a novel clinical condition. Criteria for diagnosis include biliary symptoms in the absence of gallstones but with a high gallbladder ejection fraction on cholescintigraphy (HIDA scan). Most studies use an ejection fraction above 80% as a cut-off for a gallbladder hyperkinesia diagnosis, but variations in cholescintigraphy methodology can affect the reading. Here, we report a previously undescribed effect where longer fasting times diminish the ejection fraction in gallbladder hyperkinesia patients, that could be explained by presumable gallbladder overdistention that impedes contraction.

*Methods:* We report a retrospective series of 7 patients whose clinical presentation was suspicious for symptomatic gallbladder hyperkinesia, based on 12 most common symptoms and signs of gallbladder hyperkinesia that we previously identified, but whose gallbladder ejection fraction was less than 80%. We recognized that these 7 patients had all been fasted overnight prior to cholescintigraphy. We therefore repeated cholescintigraphy with only 4 to 6 hours of fasting.

*Results:* The repeat cholescintigraphy showed a 94% increase in mean ejection fraction from 46.5% to 90.3% when fasting time was shorter, compared to initial cholescintigraphy done with overnight fasting (Paired t-test,  $p = 0.0017$ ). Six of the 7 patients opted for cholecystectomy and showed substantial symptom improvement and abnormal pathologic findings. One patient with manageable symptoms opted for medical management with dietary control.

*Conclusions:* Gallbladder ejection fractions from cholescintigraphy done after overnight fasting are diminished and thus misrepresent gallbladder contractility in gallbladder hyperkinesia patients. Cholescintigraphy using shorter fasting times provides more consistent data on gallbladder contractility in these cases. National guidelines for cholescintigraphy need redefinition, especially in the context of gallbladder hyperkinesia.

## Introduction:

The University of Iowa Gallbladder Dysfunction Clinic, founded in 2017, grew into a tertiary referral center for patients with benign gallbladder disease. Complex cases, such as aborted cholecystectomies, high surgical risk candidates, and undiagnosed upper abdominal pain were sent to us from other departments and outside hospitals for evaluation and treatment. In 2018, we independently identified symptomatic gallbladder hyperkinesia as a novel clinical condition<sup>1,2</sup>. In a comprehensive review article in early 2023, we characterized its clinical presentation and labeled it with the acronym "CASPER Gallbladder" – *Chronic Acalculous Symptomatic hyperkinetic gallbladder*<sup>1</sup>. We recognized and defined the twelve most common signs and symptoms of the CASPER gallbladder<sup>1</sup>, noted the deviations of this twelve-point checklist from the Rome IV Criteria for functional gallbladder disorders<sup>3,4</sup>, and emphasized that The Rome Foundation<sup>4,5</sup> has yet to recognize the symptomatic hyperkinetic gallbladder as a clinical entity<sup>1</sup>. We tabulated twenty-two articles and seven abstracts from the medical literature that elucidate the beneficial effects of cholecystectomy for symptomatic gallbladder hyperkinesia<sup>1</sup>.

The diagnostic triad for the CASPER gallbladder includes<sup>1,2</sup>:

- biliary symptoms,
- absence of gallstones on ultrasound, and
- a high gallbladder ejection fraction on cholescintigraphy (<sup>99</sup>Technitium-labelled Hepatobiliary Iminodiacetic Acid scan or HIDA scan).

The most common cut-off used in previous publications for a diagnosis of symptomatic

gallbladder hyperkinesia was a gallbladder ejection fraction higher than 80%<sup>1,2,6,7</sup>, although a few studies have used a cut-off level of 75%<sup>8</sup> – or even 65%<sup>1,9</sup>.

In the present study, we report a series of seven patients referred to the University of Iowa Gallbladder Dysfunction Clinic in 2023 with a constellation of symptoms and signs highly consistent with our clinical characterization of the CASPER gallbladder<sup>1,2</sup> but whose HIDA scan gallbladder ejection fractions were lower than 80%. Suspecting a skewed HIDA scan ejection fraction result, we evaluated the HIDA scan methodology in each of these seven patients and elicited the common finding that they had all fasted overnight (11-14 hours) prior to the HIDA scan instead of our preferred protocol of 4 – 6 hours of fasting. Therefore, as elaborated in the present report, we repeated the HIDA scan with fasting periods no longer than 4 – 6 hours and saw an impressive and statistically significant increase in gallbladder ejection fraction in all seven patients, permitting a diagnosis of the CASPER gallbladder. Six of these patients underwent cholecystectomy with successful relief of symptoms, while one patient opted for medical management. Our results indicate that prolonged fasting prior to cholescintigraphy suppresses gallbladder ejection fraction and hinders the diagnosis of the CASPER gallbladder.

## Methods

We performed a retrospective analysis of patients referred in 2023 in whom we ordered a repeat HIDA scan due to questions about their initial HIDA scan methodology involving overnight fasting. A repeat HIDA scan was ordered with specific written instructions in the electronic order, and verbal explanation

to the patient, to strictly use a 4- to 6-hour period of fasting and thereby avoid overnight fasting prior to gallbladder ejection fraction determination. Patients were instructed to eat a moderate-size meal about 4 to 4.5 hours before the scheduled time of the HIDA scan procedure, and to remain strict *Nil Per Oral* (NPO) without drinking even clear liquids including water. All repeat HIDA scans were performed as per our Nuclear Medicine Division protocol in 2023, which consisted of radioisotope Technetium-99m mebrofenin 5.0-5.6 mCi given IV, a basal scan done over 60 minutes, followed by gallbladder ejection fraction digital computation with IV infusion of cholecystinin octapeptide (CCK-8) analog sincalide (Kinevac, Bracco Diagnostics Inc., NJ) 0.02 mcg/kg over 30 minutes<sup>10</sup>.

Based on the repeat HIDA scan result, a detailed discussion was undertaken with each patient, they were provided our 2023 review article on the CASPER gallbladder<sup>1</sup>, and cholecystectomy was offered as a potential option for relief of bothersome symptoms affecting overall health, quality of life, employment, family life, or education. All patients received routine post-operative follow-up.

The necessary Institutional Review Board authorizations were obtained to perform this retrospective study. Statistical computations employed the Two-tailed Paired t-test to compare the initial overnight fasting HIDA scan ejection fraction result to the repeat 4- to 6-hour fasting HIDA scan ejection fraction result ( $p < 0.05$ ).

## Results

### *PATIENTS:*

We identified seven patients (Table 1) where we had evaluated the patient at the University

of Iowa Gallbladder Dysfunction Clinic, believed that the patient may have a CASPER gallbladder based on clinical presentation, suspected that the initial HIDA scan ejection fraction reading was skewed low due to prolonged fasting, and so ordered a repeat HIDA scan with no more than 4 - 6 hours of fasting. These seven patients showed a mean age of 37 ( $\pm 13$ , range 24 - 58) years, mean BMI of 31 ( $\pm 6$ , range 25 - 42) kg/m<sup>2</sup>, and a gender distribution of 5 females and 2 males.

### *OTHER VARIATIONS IN CHOLESCINTIGRAPHY METHODS:*

The initial HIDA scan was done using CCK-analog sincalide 0.02 mcg/kg IV to stimulate the gallbladder in three patients, while in the remaining four patients an oral meal (Ensure or corn oil) was used instead of CCK (Table 1). The repeat HIDA scan that we ordered was done using CCK-analog sincalide 0.02 mcg/kg IV to stimulate the gallbladder in all seven patients.

### *EFFECT OF SHORTER FASTING ON GALLBLADDER EJECTION FRACTION WITH REPEAT CHOLESCINTIGRAPHY:*

The initial gallbladder ejection fraction in the seven patients after overnight fasting was a mean of 46.5% ( $\pm 21.6\%$ , range 10 - 70%), while the repeat ejection fraction in these same patients after only 4 - 6 hours of fasting was a mean of 90.3% ( $\pm 10.1\%$ , range 71 - 99%)(Table 1). In each of these seven cases, there was an increase in the gallbladder ejection fraction after limiting fasting to only 4 - 6 hours for the repeat HIDA scan, the average difference showing a 94% increase over the initial average ejection fraction (Table 1).

TABLE 1: GALLBLADDER EJECTION FRACTION AFTER REPEAT HIDA SCAN IN 7 PATIENTS

Initial HIDA scan							Repeat HIDA scan			Management	
	Age Sex	BMI kg/m <sup>2</sup>	Location /Year	Gallbladder stimulation	NPO (hr)	GBEF (%)	Location / Year	NPO (hr)	GBEF (%)	Cholecyst ectomy	Outcome
1	51 F	25	UIHC 2023	Sinclairide 0.02 mg/kg IV infusion over 30 mins	12	70	UIHC 2023	5	98	Yes	Symptoms improved substantially. <i>Pathology:</i> Focal cholesterolosis. No gallstones/sludge.
2	36 F	42	Outside Hospital 2023	Sinclairide 0.02 mg/kg IV infusion over 30 mins	11	65	UIHC 2023	4	95	Yes	Symptoms improved substantially. <i>Pathology:</i> Mild chronic cholecystitis, Cholesterolosis. No gallstones/ sludge.
3	28 F	29	UIHC 2023	Sinclairide 0.02 mg/kg IV infusion over 30 mins	12	35	UIHC 2023	5	71	Yes	Symptoms improved substantially. <i>Pathology:</i> Chronic cholecystitis. No gallstones/sludge.
4	36 M	29	UIHC 2022	Corn oil emulsion 30 cc (Note: CCK shortage in 2022)	12	60	UIHC 2023	5	90	Yes	Symptoms improved substantially. <i>Pathology:</i> Chronic cholecystitis. No gallstones/sludge.
5	24 F	25	Outside Hospital 2022	Ensure 8 oz	14	54	UIHC 2023	6	98	Yes	Symptoms improved substantially. <i>Pathology:</i> Enlarged cystic lymph node seen at surgery. Erythema at the fundus. No gallstones/sludge.
6	58 F	33	Outside Hospital 2016	Ensure 8 oz	12	32	Outside Hospital 2024	4	83	Yes	Symptoms improved substantially. <i>Pathology:</i> Chronic cholecystitis and cholesterolosis. No gallstones /sludge.
7	25 M	34	Outside Hospital 2023	Ensure 8 oz	14	10	UIHC 2023	5	99	No	Symptoms in status quo (opted for medical management due to mild symptoms)

**TABLE 1 Legend:** A total of 7 patients had a repeat HIDA scan done after only 4 to 6 hours of fasting and CCK analog sinclairide 0.02 mg/kg IV infusion over 30 minutes, following an initial HIDA scan done after overnight (11 to 14 hours) fasting. In all patients, ultrasound did not show gallstones or sludge. The repeat HIDA scan showed a 94% increase in mean GBEF from 46.5% to 90.3% when fasting time was shorter, compared to the initial HIDA scan with overnight fasting. BMI: Body mass index. NPO: Nil Per Oral. GBEF: Gallbladder Ejection Fraction. UIHC: University of Iowa Hospitals & Clinics, Iowa City, IA.

The Two-tailed Paired t-test comparing the differences between the two readings in the seven subjects showed that the probability of the increase in ejection fraction with shorter fasting being merely due to chance was very low ( $p < 0.05$ ), as shown below:

1. *All seven patients taken together (patients #1 to #7):*

The increase in Gallbladder Ejection Fraction seen in all 7 patients taken together was statistically significant ( $p = 0.0017$ ).

2. *Cholecystokinin (CCK) analog-stimulated group only (patients #1 to #3):*

When only the 3 patients given CCK-analog in the initial HIDA scan were compared to that of the repeat HIDA scan, the increase in GBEF was still significant ( $p = 0.006$ ).

3. *Meal-stimulated group only (patients #4 to #7):* When only the 4 patients given an oral meal instead of CCK analog in the first HIDA scan were compared to that of the repeat HIDA scan, the increase in GBEF was still significant ( $p = 0.025$ ).

In summary, all seven patients showed a significant increase in gallbladder ejection fraction when the pre-HIDA scan fasting period was shortened to 4 - 6 hours, irrespective of whether the initial overnight fasting scan was done with CCK or an oral meal.

#### **TREATMENT:**

Out of the seven patients, six opted for cholecystectomy after the repeat HIDA scan, while one preferred medical management with dietary control. Laparoscopic cholecystectomy was performed as a same-day-surgery on the six patients wanting surgery, there were no surgical complications, and they experienced substantial

amelioration of their symptoms with associated improvements in daily functionality and quality of life. The patient that opted for non-surgical management continued in status quo with his predominant symptom being diarrhea that was apparently manageable.

#### **Discussion:**

Our findings in the present study indicate that prolonged periods of pre-HIDA scan fasting significantly diminish the gallbladder ejection fraction in patients with symptomatic gallbladder hyperkinesia. We have shown that in seven consecutive patients with overnight fasting prior to initial HIDA scan which had ejection fractions incompatible with a diagnosis of a CASPER gallbladder — although their clinical presentation was suspicious for CASPER gallbladder — a repeat HIDA scan with only 4 to 6 hours of fasting showed a significantly higher gallbladder ejection fraction that justified offering cholecystectomy for symptomatic gallbladder hyperkinesia.

This is a preliminary report with a limited number of patients, but the phenomenon needs clinician awareness to minimize additional delays in patients suffering from this undiagnosed clinical condition. Clinicians need to be aware that a diagnosis of the CASPER gallbladder can be missed if standardized HIDA scan protocols are not followed. Over time, larger populations of patients should be studied at different medical centers to delve deeper into the preliminary findings of our present study to see how wide variations in HIDA scan ejection fraction measurements can be limited by reducing the number of variables in HIDA scan methodology.

Wide variation in HIDA scan protocols renders national standardization difficult and data comparisons inconsistent<sup>10-16</sup>. The more differences there are in HIDA scan protocols the more confusion there will be with the diagnosis and definition of a novel clinical entity such as the CASPER gallbladder. In addition to variations in HIDA scan fasting time emphasized in the present study, the use of oral meals instead of IV CCK adds additional variables<sup>11</sup>. Gastric emptying times show much variation in healthy and diseased (e.g., diabetes mellitus, gastroparesis) individuals resulting in more vagaries in gallbladder ejection fraction results when compared to the use of a continuous intravenous infusion of CCK over 30 to 60 minutes<sup>10,11</sup>. Delayed gastric emptying, often idiopathic, can postpone gallbladder stimulation after a meal and thus suppress gallbladder ejection fraction values<sup>10</sup>. Proponents of the use of oral meals to stimulate the gallbladder during HIDA scan promote the cost benefit over the use of intravenous CCK. However, a missed diagnosis of the CASPER gallbladder and the difficulty in comparing patient data add much more expense to the healthcare system, to society, and to the patient, even beyond mere monetary costs. If a HIDA scan has to be repeated due to a questionable protocol, any argument regarding cost benefit becomes moot. Additionally, asking a patient already suffering with nausea, vomiting, or abdominal pain that is worsened by food to consume a fatty meal can be an irksome experience for the patient. The classic 2002 paper by G. T. Krishnamurthy et al., the only paper to compare intravenous CCK and a fatty meal on two separate HIDA scans done on

consecutive days in the same healthy volunteer — with a reasonable sample size (n = 13) — showed that a fatty meal is associated with a longer latent period and ejection period, a lower ejection fraction, and greater variability of ejection fractions, compared to intravenous CCK infusion<sup>11</sup>.

Cholescintigraphy protocols using CCK as an intravenous bolus or as a short 15-minute intravenous infusion are associated with marked variations in gallbladder ejection fraction, compared to 30 to 60-minute intravenous CCK infusions, and are therefore discouraged by the Society of Nuclear Medicine & Molecular Imaging (SNMMI) Practice Guideline for cholescintigraphy<sup>10-16</sup>. Additionally, intravenous doses of CCK given over durations shorter than 30 minutes are associated with abdominal cramping and nausea even in healthy volunteers.

The SNMMI Practice Guideline for HIDA scan published in 2010<sup>14</sup> recommends fasting for at least 2 hours, but preferably 6 hours, prior to HIDA scan. However, the recommendations do not specify an upper limit of fasting time and only state that fasting longer than 24 hours may result in non-filling of the gallbladder. The 2010 SNMMI guidelines were proposed in the context of the investigation of a non-filling gallbladder in the diagnosis of acute cholecystitis to confirm cystic duct obstruction and decide surgical treatment in questionable emergency cases. The guidelines did not make any specific recommendations in relation to maximum fasting times for HIDA scans done to investigate motility disorders of the gallbladder. There have been no previous studies, to our knowledge, that compared

overnight fasting to 4 – 6 hours of fasting either in healthy volunteers or in gallbladder dysmotility patients to standardize HIDA scan protocols<sup>10,12-14,16-19</sup>. Similarly, even the 2010 SNMMI guideline for a minimum 2-hour fast prior to HIDA scan may apply to the investigation of a non-filling gallbladder for acute cholecystitis, but a minimum of 4 hours fasting would be needed in the determination of gallbladder ejection fraction after gallbladder filling. This is because any meal 2 hours prior to HIDA scan could result in premature gallbladder contraction during the initial hour of basal scanning for gallbladder filling even before CCK is given. The SNMMI guidelines of 2010 were laid down before the first paper on hyperkinetic gallbladders was published in 2012<sup>20</sup>. The new evidence in the present study suggests that the SNMMI guidelines need to be revisited in the setting of the diagnosis of the CASPER gallbladder: the upper limit of pre-HIDA scan fasting should be restricted to 6 hours rather than 24 hours, while the lower limit should be at least 4 hours rather than 2 hours.

Based on the findings of our present study, we hypothesize that a combination of gallbladder overdistention and increased gallbladder bile viscosity from overnight fasting impedes gallbladder contraction in response to stimulation and thereby artificially lowers the gallbladder ejection fraction measurement. Overdistention increases gallbladder wall tension due to increased sphere size and thinned-out wall as, according to Laplace's Law<sup>21,22</sup>, the tension in the wall of a sphere is directly proportional to its radius and inversely proportional to wall thickness. Therefore, the gallbladder wall smooth muscle will have to overcome the higher wall tension while

attempting to contract when stimulated by CCK in the overdistended state. Second, overnight fasting also increases the viscosity of bile due to the physiological process of water absorption by the gallbladder wall mucosal lining which concentrates the bile. Applying the laws of fluid dynamics laid down by Poiseuille<sup>23</sup>, the volume flow rate of bile is decreased from a gallbladder that contains bile of higher viscosity. Third, from a physiological perspective, stretching of the gallbladder wall smooth muscle from overdistention can weaken its contractile force.

Our patient-centered clinical approach in evaluating, diagnosing, and treating patients at the University of Iowa Gallbladder Dysfunction Clinic between 2017 and 2022 provided insights to define the twelve most common presenting symptoms and signs of the CASPER gallbladder by early 2023<sup>1</sup>. We were thereby able to identify patients suspected of suffering from the CASPER gallbladder based purely on clinical manifestations elicited with a focused history and examination. So, when certain patients had a clinical presentation consistent with a diagnosis of the CASPER gallbladder but had a HIDA scan showing a relatively low ejection fraction, we had gained sufficient confidence to query potential deviations in the HIDA scan protocol that may have negatively impacted the gallbladder ejection fraction reading. It was, in effect, an ongoing Quality Improvement project. In this manner, we came across a series of consecutive patients where overnight fasting was associated with lower than clinically projected gallbladder ejection fractions, while the repeat HIDA scan with 4 – 6 hours of fasting returned a substantially higher reading. By early 2024,

we identified a series of seven patients fitting the pattern that we had identified, and ran statistical comparisons to confirm that the trend was significant, prompting this preliminary report. Future studies with larger numbers, in patients in whom the presenting clinical picture does not correlate with the initial HIDA scan gallbladder ejection fraction, should involve more medical centers and use a planned and prospective approach with well-defined HIDA scan protocols for the repeat study.

Symptomatic improvement of pre-operative symptoms in the six patients that underwent cholecystectomy was consistent with previous reports<sup>1,2,6,7,24-31</sup>, as all six expressed substantial satisfaction with symptom amelioration after surgery leading to much improved daily functioning. Patient #7's clinical presentation and repeat gallbladder ejection fraction of 99% made him eligible for cholecystectomy (Table 1), but he opted for non-operative management as his symptoms were manageable.

Symptoms of severe nausea or vomiting can interfere with the oral intake needed until 4 - 6 hours prior to the HIDA scan, as was seen in Patient #3, where the gallbladder ejection fraction went up to only 71% (from 35%). Patient #3 was able to take only a couple of tablespoons of food 4 hours prior to her repeat HIDA scan, which may have been insufficient to stimulate adequate gallbladder emptying. Taking this into consideration, and aware that some papers have used a gallbladder ejection fraction greater than 65% as their cut-off for a diagnosis of gallbladder hyperkinesia<sup>9,32</sup>, the patient was offered surgery due to her chronic symptoms of eight years duration. She was keen on proceeding

with cholecystectomy as a working mother caring for a young child, and as five months had passed since her initial HIDA scan.

Future questions:

- Does the fasting period for HIDA scan also affect gallbladder ejection fraction in healthy volunteers?
- Does overnight fasting have a greater negative impact on ejection fractions in CASPER gallbladder patients than in healthy volunteers?
- Does an unduly long period of fasting for HIDA scan also skew the ejection fraction result in patients with gallbladder hypokinesia?

The effect of prolonged fasting times may have a detrimental impact mainly on the diagnosis of symptomatic hyperkinesia, as ejection fractions from hyperkinetic gallbladders could be skewed downwards into the normal range.

Our recommended cholescintigraphy protocol for gallbladder motility disorders:

1. Recognize the indication for cholescintigraphy: The order for the HIDA scan should indicate that gallbladder ejection fraction measurement is required to evaluate gallbladder motility disorders such as hypokinesia<sup>33</sup> or hyperkinesia. Simple gallbladder filling, without stimulation, to exclude acute cholecystitis is not the objective of the study.
2. Routinely plan for only 4 - 6 hours of fasting prior to cholescintigraphy: Patient instructions should specify that fasting should be no longer than 6 hours, and no shorter than 4 hours, prior to checking in for the HIDA scan. Too long or too short periods of fasting can skew the ejection fraction reading.



3. No clear liquids during fasting: The instructions for 4 – 6 hours of fasting should clarify that no clear liquids – not even water – are allowed during the 4 – 6 hours of fasting (except for essential medications). This is because even gastroduodenal distension from drinking too much clear liquid can induce premature spontaneous gallbladder contraction.

4. Sixty minutes of baseline scanning: The 2010 SNMMI guideline to allow 60 minutes after IV radionuclide injection to evaluate gallbladder filling should be continued.

5. Cholecystokinin (CCK) infusion no shorter than 30 minutes: Use CCK infusion (sincalide) 0.02 mcg/kg over a 30- to 60-minute infusion to calculate the ejection fraction to stimulate gallbladder contraction, as recommended by SNMMI [do not use oral meals (corn oil, Ensure, full cream milk) due to difficulties in standardization<sup>11</sup>].

6. Use the standard equation to calculate ejection fraction<sup>12,15,34</sup>: The Gallbladder ejection fraction on HIDA scan should be calculated from the maximum level to the lowest level of gallbladder radioactivity counts and not from the beginning to the end of CCK infusion or scanning.

## Conclusions

1. Overnight fasting prior to HIDA scan suppresses the gallbladder ejection fraction and thus skews the result sufficiently to hinder a diagnosis of the CASPER gallbladder.

2. Evaluation of motility disorders of the gallbladder with HIDA scans should avoid prolonged fasting, beyond six hours, prior to testing.

National guidelines for HIDA scan protocols need redefinition in this context, as current protocols allow up to 24 hours of pre-HIDA scan fasting and were defined at a time when no articles on the CASPER gallbladder were yet published.

## Conflict of Interest:

None

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None

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