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EDITORIAL

Cholescintigraphy protocols for the Chronic Acalculous Symptomatic Hyperkinetic Gallbladder: Fantasies, fallacies, and unsolved mysteries!

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ABSTRACT

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Introduction:

*The **C**hronic **A**calculous **S**ymptomatic hy**PER**kinetic* **(CASPER)** Gallbladder is not yet recognized as a clinical entity.[1] The CASPER gallbladder, diagnosed with a high gallbladder ejection fraction on cholescintigraphy (HIDA scan), typically produces symptoms such as pain after a fatty meal.[1,2] A gallbladder ejection fraction of 80% or above on cholescintigraphy is generally used as a cut-off level for diagnosis.[1,2] Two recent publications have raised a controversy about the usefulness of cholescintigraphy in the diagnosis of gallbladder motility disorders, one supporting it[3] and the other questioning it.[4] However, a third publication has shown that cholescintigraphy protocols used for motility disorders of the gallbladder lack standardization and, therefore, any discussions or conclusions about the topic would be rendered moot.[5] This Editorial emphasizes the need for a general consensus for uniformity of protocols employed for cholescintigraphy in the investigation and diagnosis of motility disorders of the gallbladder.

Fantasies, Fallacies, Unsolved Mysteries

Fantasies are illusions, fallacies are delusions, unsolved mysteries are hidden collusions. Here, all three – fantasies, fallacies, and unsolved mysteries – are explored against the backdrop of a difficult-to-identify, relatively unknown, recently described clinical condition: *The CASPER gallbladder*.[1]

Symptomatic gallbladder hyperkinesia, or CASPER gallbladder, is a novel clinical entity that is not recognized by the medical community as it is not as yet featured in standard medical textbooks.[1] The essentials of diagnosis of a CASPER gallbladder are[1,2]:

a) biliary symptoms,
b) absence of gallstones on ultrasound, and
c) a high gallbladder ejection fraction on cholescintigraphy [hepatobiliary iminodiacetic acid (HIDA) scan].

As a novel condition coming into focus only in the first quarter of the 21st century,[1] certain reservations exist regarding the diagnosis of the CASPER gallbladder:

The central *fantasy*: The belief that cholescintigraphy ejection fraction results are infallible is an *illusion* because cholescintigraphy protocols are far from standardized for gallbladder motility disorders.

The central *fallacy*: Although a gallbladder ejection fraction of 80% is widely used as the cut-off for a diagnosis of CASPER gallbladder, it is a *delusion* because there is recent evidence that current cholescintigraphy protocols underestimate ejection fractions in gallbladder hyperkinesia.[5]

The central unsolved *mystery*: Whether or not symptomatic gallbladder hyperkinesia is a real clinical entity continues to be a *mystery* and, until solved, it will be brushed away as a *hidden collusion* between patients and their physicians.

Defining An "Excitable" Vs. A "Lazy" Gallbladder

The contrasting opposite to symptomatic gallbladder hyperkinesia or the *"Excitable Gallbladder" is symptomatic gallbladder hypokinesia or the "Lazy Gallbladder."*[1,2] Symptomatic gallbladder hypokinesia is a condition established in the 1980s-1990s and is defined as biliary symptoms in the absence of cholelithiasis but with a low gallbladder ejection fraction less than 40%.[6] The indication for cholecystectomy to relieve symptoms in gallbladder hypokinesia was established by a randomized trial in 1991.[6] In 22 publications reporting the beneficial effects of cholecystectomy for symptomatic gallbladder hyperkinesia from 2012 to 2022, the ejection fraction cut-off level for diagnosis ranged from as low as 65% up to 80%.[1] Importantly, in all these papers, the selection of the gallbladder ejection fraction cut-off level was *entirely arbitrary*.

Defining "Excitable" Ejection Fraction: The First Exploration

For this reason, the recent study led by Professor James A. Madura, II, MD, FACS (Mayo Clinic, Phoenix, AZ), is a profound and timely report that illuminates an otherwise obscure area.[3] Dr. Madura and his team collected gallbladder ejection fraction data from 2,929 cholescintigraphy studies done in adults at the 3 Mayo Clinics (Rochester, MN, Gainesville, FL, & Phoenix, AZ) from 2007-2020, and did detailed statistical analyses to query the gallbladder ejection fraction cut-off level for a diagnosis of gallbladder hyperkinesia that benefitted from cholecystectomy. They identified

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141 patients that underwent cholecystectomy whose ejection fraction was above 50% and showed that patients with ejection fractions ≥ 81% had resolution of pain in 78% of patients, while those with ejection fractions between 50% and 80% had pain resolution in only 60%. They suggest that a gallbladder ejection fraction cut-off of 81% is a reasonable upper limit of normal gallbladder contractility. They recommend cholecystectomy for symptomatic gallbladder hyperkinesia patients with an ejection fraction greater than or equal to 81%. This paper published in the Journal of the American College of Surgeons in November 2023 is indeed a landmark paper as it is the first and only study to apply credible statistical methodology to show that gallbladder ejection fractions above 80% in symptomatic patients is a reasonable cut-off level for an indication for cholecystectomy. Their work also provides support to the concept that symptomatic gallbladder hyperkinesia is a real disease and not a "mystery, fallacy, or fantasy".

However, in response to the above Mayo Clinic study, an "Invited Review" article commissioned by the Journal of the American College of Surgeons and written by Assistant Professor Eric M. Knauer, MD, FACS (Emory University, Atlanta, GA), challenged their conclusions by suggesting the opposite — that gallbladder ejection fraction measurement may have no value in patient selection for cholecystectomy in this patient population, and that HIDA scan studies are therefore of questionable "usefulness".[4] These suggestions are based on the Mayo Clinic study finding that more than half the patients with ejection fractions between 50% and 80% also had good outcomes with cholecystectomy. The argument is that if patients with gallbladder hypokinesia (low ejection fraction <40%), gallbladder hyperkinesia (ejection fraction >80%), and several patients in-between (ejection fraction 50-80%) show amelioration of symptoms with cholecystectomy, then why not do away with ejection fraction data altogether and focus mainly on patients' presenting symptomatology?

Dr. Madura's novel study and Dr. Knauer's critique of the study represent two opposing perspectives, and this Editorial examines the contradictions involved. Reading between the lines, Dr. Knauer's comments raise a hidden question: Does symptomatic gallbladder hyperkinesia really exist or is it merely a figment of the imagination? It also raises a pertinent question: Should we stop performing cholescintigraphy altogether and rely entirely on symptoms? But the *fallacy* here is the *fantasy* that cholescintigraphy protocols done for motility disorders of the gallbladder are "perfect" — they are far from it. Surprisingly, no one has yet designed a cholescintigraphy protocol that takes into consideration the unique aspects of gallbladder hyperkinesia (or even hypokinesia) and, therefore, ejection fraction results are skewed. This *unsolved mystery* also impacts the Mayo clinic conclusion that 81% is the ejection fraction cut-off for gallbladder hyperkinesia as, although their statistical method was relevant, the raw data used is questionable. Due to a lack of standardization, inherent variations in cholescintigraphy protocols will twist ejection fraction readings and thus contaminate any analytic interpretations thereof.

Refining Cholescintigraphy Protocols for Motility Disorders

At *The University of Iowa Gallbladder Dysfunction Clinic*,[1,2,5] founded in 2017, patients are referred to us from within and outside Iowa. We identified specific aspects of cholescintigraphy protocols, with wide variations in methodology, that impact the ejection fraction reading.[5] A part of the central *fallacy* is that although gallbladder ejection fraction is key to the diagnosis of the CASPER gallbladder, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines for cholescintigraphy[7] available on their website since 2010 were laid down before the first paper on symptomatic hyperkinetic gallbladder was published in 2012.[1,8] We underline several points about existing cholescintigraphy protocols used at various medical centers that impact gallbladder ejection fraction readings and skew the results, especially in a downward direction. We emphasize that without a new systematic standardized cholescintigraphy protocol to measure gallbladder ejection fraction no logical and reliable data analysis can be done.[5] In chronologic order, these are the steps of cholescintigraphy protocols that reduce gallbladder ejection fraction measurements:

1. **Fasting period before cholescintigraphy:** Prolonged (overnight) fasting impedes gallbladder emptying reducing gallbladder ejection fraction. Instead, fasting should not exceed a 6-hour period. Additionally, the fasting period: a) should not be

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shorter than 4 hours, to allow time for the gallbladder to refill, and b) should not allow liquids — not even water — to prevent gastric distention from excess fluid intake which can induce premature gallbladder emptying.

2. **Method of stimulating gallbladder contraction:** Enteral feeding (e.g., solid meal, Ensure drink, milk cream, corn oil) to stimulate gallbladder contraction is weaker and less consistent than intravenous cholecystokinin (CCK) infusion.[9]

3. **Method of administering CCK to stimulate the gallbladder:** Intravenous CCK given over short time periods to stimulate gallbladder contraction is weaker and less consistent than intravenous CCK infusions over 30 to 60 minutes.[10,11]

4. **Reading the gallbladder ejection fraction graph:** The cholescintigraphy graph for ejection fraction should take the highest point and lowest point for computing the ejection fraction and not the beginning point and end point.[7,12]

We found evidence in the literature, and in our clinical practice,[5] that any one or more of these protocol variations can result in a lower gallbladder ejection fraction than otherwise if a disciplined cholescintigraphy protocol is not followed.[5] The most common factor that results in a negatively skewed gallbladder ejection fraction is overnight fasting[5] as SNMMI guidelines do not restrict fasting periods, even for motility disorders of the gallbladder, but allow up to 24 hours of fasting prior to cholescintigraphy.[7] The SNMMI guidelines, originally intended for diagnosis of a non-filling gallbladder to diagnose acute cholecystitis, have not been adjusted to accommodate the physiology and physics involved in gallbladder contraction.[5] Prolonged fasting results in gallbladder overdistention and increased viscosity of bile from water reabsorption — both of which impede gallbladder contraction in response to stimulation.[5]

Therefore, unless national guidelines for cholescintigraphy conform to the requirements essential for relatively more accurate measurements of gallbladder ejection fraction for gallbladder motility disorders, the gray area that lies between Dr. Madura's 2023 paper and Dr. Knauer's critique cannot be clarified or even intelligently discussed. Specifically, the gallbladder ejection fraction cut-off level for a diagnosis of gallbladder hyperkinesia and the role of cholescintigraphy in the evaluation of symptomatic gallbladder motility disorders cannot be determined if cholescintigraphy protocols are fundamentally flawed. *Until valid cholescintigraphy protocols are standardized and followed, the illusions of fantasy, the delusions of fallacy, and the hidden collusions of the unsolved mystery of the symptomatic hyperkinetic gallbladder will mire the field and perpetuate confusion.*

Conclusion

Guidelines for cholescintigraphy protocols to investigate motility disorders of the gallbladder, such as symptomatic gallbladder hypokinesia and hyperkinesia, need to be reassessed and revised to be relevant in the unique physiological context of these diseases. Without a profound reevaluation and amendment of cholescintigraphy protocols that lead to standardization, sufficient progress cannot be made in the investigation, characterization, and management of gallbladder motility disorders.

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Conflict of Interest

None.

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References

1. Samuel I. The chronic acalculous symptomatic hyperkinetic (CASPER) gallbladder or "The Excitable Gallbladder". *JSM Gastroenterol Hepatol*. 2023;10(1):1113. Doi: 10.47739/2373-9487/1113.
2. Pillenahalli Maheshwarappa R, Menda Y, Graham MM, Boukhar SA, Zamba GKD, Samuel I. Association of gallbladder hyperkinesia with acalculous chronic cholecystitis: A case-control study. *Surgery*. 2020;168(5):800-8. Doi: 10.1016/j.surg.2020.06.005.
3. Kartik A, Jorge IA, Webb C, Lim ES, Chang YH, Madura J. Defining Biliary Hyperkinesia and the Role of Cholecystectomy. *J Am Coll Surg*. 2023;237(5):706-10. Doi:10.1097/XCS.0000000000000793.
4. Knauer EM. Invited Commentary: Treatment Guidance for Patients with Hyperkinetic Gallbladder. *J Am Coll Surg*. 2023;237(5):710-1. Doi: 10.1097/XCS.0000000000000811.
5. Samuel I. Negative impact of prolonged fasting on gallbladder ejection fraction measurement with cholescintigraphy in Chronic Acalculous Symptomatic hyPERkinetic (CASPER) gallbladders. *Medical Research Archives*. 2024;12(3). Doi: 10.18103/mra.v12i3.5129.
6. Yap L, Wycherley AG, Morphett AD, Toouli J. Acalculous biliary pain: cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. *Gastroenterology*. 1991;101(3):786-93. Doi:10.1016/0016-5085(91)90540-2.
7. Tulchinsky M, Ciak BW, Delbeke D, et al. SNM practice guideline for hepatobiliary scintigraphy 4.0. *J Nucl Med Technol*. 2010;38(4):210-8. Doi: 10.2967/jnmt.110.082289.
8. DuCoin C, Faber R, Ilagan M, Ruderman W, Wier D. Normokinetic biliary dyskinesia: a novel diagnosis. *Surg Endosc*. 2012;26(11):3088-93. Doi: 10.1007/s00464-012-2342-0.
9. Krishnamurthy GT, Brown PH. Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction. *J Nucl Med*. 2002;43(12):1603-10.
10. Ziessman HA, Tulchinsky M, Lavely WC, et al. Sincalide-stimulated cholescintigraphy: a multicenter investigation to determine optimal infusion methodology and gallbladder ejection fraction normal values. *J Nucl Med*. 2010;51(2):277-81. Doi:10.2967/jnumed.109.069393.
11. Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. *J Nucl Med*. 1992;33(4):537-41.
12. Krishnamurthy GT, Bobba VR, Kingston E. Radionuclide ejection fraction: a technique for quantitative analysis of motor function of the human gallbladder. *Gastroenterology*. 1981;80(3):482-90.

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