Use of Real-Time Cine MRI to Assess the Respirophasic Variation of the Inferior Vena Cava—Proof-of-Concept and Validation Against Transthoracic Echocardiography

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Background: In clinical practice, the right heart filling status is assessed using the respirophasic variation of the inferior vena cava (IVC) assessed by transthoracic echocardiography (TTE) showing moderate correlations with the catheter-based reference standard.

Purpose: To develop and validate a similar approach using MRI.

Study Type: Prospective.

Population: 37 male elite cyclists (mean age 26 ± 4 years).

Field Strength/Sequence: Real-time balanced steady-state free-precession cine sequence at 1.5 Tesla.

Assessment: Respirophasic variation included assessment of expiratory size of the upper hepatic part of the IVC and degree of inspiratory collapse expressed as collapsibility index (CI). The IVC was studied either in long-axis direction (TTE) or using two transverse slices, separated by 30 mm (MRI) during operator-guided deep breathing. For MRI, in addition to the TTE-like diameter, IVC area and major and minor axis diameters were also assessed, together with the corresponding CIs.

Statistical Tests: Repeated measures ANOVA test with Bonferroni correction. Intraclass correlation coefficient (ICC) and Bland–Altman analysis for intrareader and inter-reader agreement. A P value <0.05 was considered statistically significant.

Results: No significant differences in expiratory IVC diameter were found between TTE and MRI, i.e., 25 ± 4 mm vs. 25 ± 3 mm ($P = 0.242$), but MRI showed a higher CI, i.e., $76\% \pm 14\%$ vs. $66\% \pm 14\%$ ($P < 0.05$). As the IVC presented a noncircular shape, i.e., major and minor expiratory diameter of 28 ± 4 mm and 21 ± 4 mm, respectively, the CI varied according to the orientation, i.e., $63\% \pm 27\%$ vs. $75\% \pm 16\%$, respectively. Alternatively, expiratory IVC area was 4.3 ± 1.1 cm^2 and showed a significantly

higher CI, i.e., 86% ± 14% than diameter-based CI ($P < 0.05$). All participants showed a CI >50% with MRI versus 35/37 (94%) with TTE. ICC values ranged 0.546–0.841 for MRI and 0.545–0.704 for TTE.
Conclusion: Assessment of the respirophasic IVC variation is feasible with MRI. Adding this biomarker may be of particular use in evaluating heart failure patients.
Level of Evidence: 1
Technical Efficacy Stage: 2

Assessment of central venous pressure (CVP) is important in the evaluation of the hemodynamic status of, for example, patients with heart failure (HF) or pulmonary hypertension.[1–5] Moreover, in conditions where the left ventricular (LV) filling pressure cannot be adequately measured, CVP estimates yield prognostic value.[3,4] Catheter-based measurement of right atrial pressure (RAP) remains the reference standard.[6–9] In clinical practice, however, CVP is estimated at transthoracic echocardiography (TTE) assessing the respirophasic variation of the inferior vena cava (IVC) by means of the expiratory IVC diameter (*d*) and its degree of collapsibility (collapsibility index (CI)) during inspiration or alternatively using a sniff-test.[6–10] The rationale is that the IVC, as a highly compliant vessel not separated from the right atrium by a valve, immediately feels the adverse effects of a rise in RAP. In normal conditions, the IVC has its maximal size in expiration and decreases substantially, or collapses completely, during inspiration or when provoked using a sniff-test. In conditions with increased right heart filling pressures, the IVC is dilated and shows diminished or absent inspiratory collapsibility. TTE estimates correlate moderately well with invasively measured RAP.[5,6] Moreover, a combination of expiratory IVC diameter and CI allows stratification of patients into those with normal, intermediate, or high RAP.[10] To standardize measurements, a subcostal view using a longitudinal direction is recommended by the American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI).[10]

MRI is increasingly used in assessing and phenotyping HF patients.[1,11] This imaging modality blends accurate quantification of cardiac volumes and function with in-depth myocardial phenotyping and myocardial perfusion imaging. An increasing number of studies have also investigated MRI-based approaches to assess left and right heart filling pressures.[12–15] Moreover, with the advent of fast cine imaging sequences, physiologic phenomena such as respiratory-phasic variation of cardiac filling can be exploited to evaluate, for example, pathologic ventricular coupling in patients with constrictive pericarditis.[16,17]

The aim of this proof-of-concept study was to explore the respirophasic variation of the IVC with real-time cine MRI and to validate MRI assessment of CI against TTE. Development of an MRI-based biomarker reflecting the patient's right heart filling status could further improve patient risk stratification and therapy planning by MRI.

Materials and Methods

This study was part of a prospective study looking at the long-term effects of endurance exercise on the heart (Pro@Heart Study—trial registration number NCT05164328—ACTRN126118000716268).[18] The study was approved by the ethical committee (S57241) and all participants gave written informed consent. The study complied with the Declaration of Helsinki. The study cohort included 38 male elite cyclists (26 ± 4 years) who underwent a comprehensive investigation, including TTE and MRI at rest and during exercise. MRI was performed immediately after the TTE exam.

TTE Study

Evaluation of the IVC with TTE was performed from the subcostal view with the patient in the supine position using a Vivid E95 ultrasound system (GE Healthcare, Horten, Norway) with a 4Vc-D matrix 4D cardiac probe. Measurements were performed at 1.0 to 2.0 cm from the junction with the right atrium, using the long-axis view.[10] The subject was instructed to deeply breathe in and breathe out while scanning the IVC.

MRI Protocol

To study the IVC with MRI, a Cartesian balanced steady-state-free-precession sequence was used with image parameters: TE/TR/flip angle of 0.80 msec/1.93 msec/50°; acquired voxel size of $3.75 \times 4.67 \times 10$ mm^3, reconstructed voxel size of $2.8 \times 2.8 \times 10$ mm^3, 360×304 mm^2 FOV, half-scan 0.625, linear profile order, 180 msec temporal resolution, 85 time-frames for a scan duration of 15 sec. Rather than studying the IVC in the long-axis direction as at TTE, we imaged the IVC in the transverse orientation using two slices positioned from a coronal scout view (acquired at end-expiration) through the upper part of the hepatic IVC (Fig. 1). As the typical craniocaudal motion of the diaphragm during deep, free breathing is ~2–3 cm, an interslice distance of 30 mm was used.[19,20] During scanning, the subject was instructed by the operator to deeply breathe in and breathe out with a relatively rapid pace, i.e., ~3–4 sec per respiratory cycle. After scanning, the cine images were checked to ensure that the upper part of the hepatic IVC was encompassed over the entire respiratory cycle and to evaluate the respiratory depth adequacy. In case of a too shallow inspiration with limited excursion of the thoracic cage, the subject was instructed again, and the acquisition was repeated.

Image Analysis

At TTE, maximal expiratory and minimal inspiratory diameter of the IVC were measured and the degree of inspiratory collapsibility, defined as CI: maximum diameter (IVC max) – minimum diameter (IVC min)/IVC max was calculated (Fig. 2 and Video S1).[10]
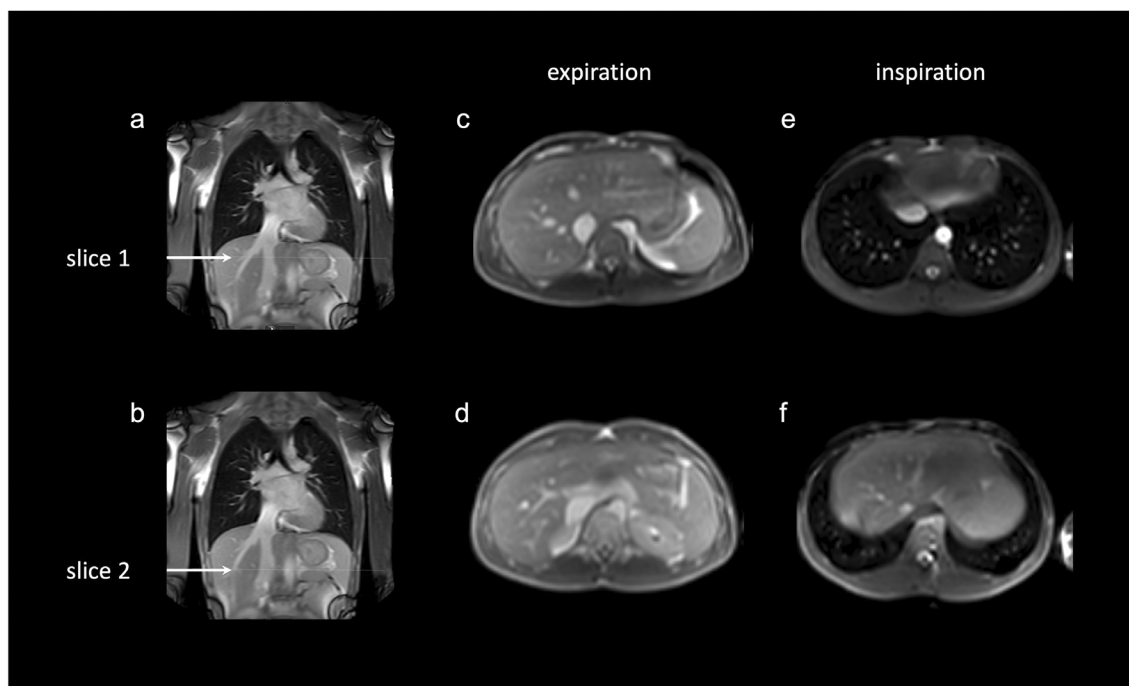
FIGURE 1: Slice positioning of real-time axial cine images. Coronal scout view acquired at end-expiration (panel a and b). Slice 1 was positioned 1–2 cm below the entrance of the hepatic veins in the IVC (panel a). Slice 2 was positioned 30 mm from slice 1, toward the feet (panel b). The respective expiratory and inspiratory images at slice 1 and slice 2 are shown in panel c and panel e, and in panel d and panel f, respectively. Whereas, slice 1 is most suitable for evaluating the IVC during expiration (panel c), due to the downward movement of the diaphragm during inspiration, slice 2 is most suitable for evaluating the upper part of the hepatic IVC during inspiration (panel f). As the normal craniocaudal motion of the diaphragm is between 2 and 3 cm, an interslice distance of 30 mm was used.

The MRI analysis was performed by an EACVI-CMR level 3 accredited reader (31 years of experience (JB)), blinded to the TTE results. First, the cine frames of the two axial slices were visually assessed to determine the timeframe with the maximal and minimal IVC size at expiration and inspiration, respectively (Fig. 1 and Video S2). At these timeframes, IVC diameter was measured using an electronic caliper along a TTE-like orientation. As the IVC cross-section was not always circular, the major and minor diameters (d) were also measured, as previously described by Seo et al. (Fig. 2).[20] Moreover, to appreciate the changes in IVC shape during the respiratory cycle, we measured the orientation of the major diameter at inspiration and expiration and calculated the angle between the two (Fig. 3 and Video S2). In addition to IVC diameter, the IVC circumference

was contoured at MRI as well allowing to quantify IVC area at expiration and inspiration (Fig. 2).[10,20,21] MRI CIs were calculated based on the IVC diameters and IVC area. The pattern of inspiratory collapse was visually assessed and defined as showing a flattened, i.e., one-dimensional or a circular, i.e., two-dimensional collapse. Finally, to relate IVC size to the aortic size, aortic diameter and area were measured in the same slice and time frame as the one used to evaluate the expiratory and inspiratory IVC. The MRI and TTE studies were independently analyzed by two different readers blinded to the other results (MRI: JB and SL/TTE: YB and TR). Experience level of SL, YB, and TR was 4, 6, and 5 years, respectively. To study the intrareader and inter-reader reproducibility of the TTE and MRI approach, all studies were reread by the same reader considering a
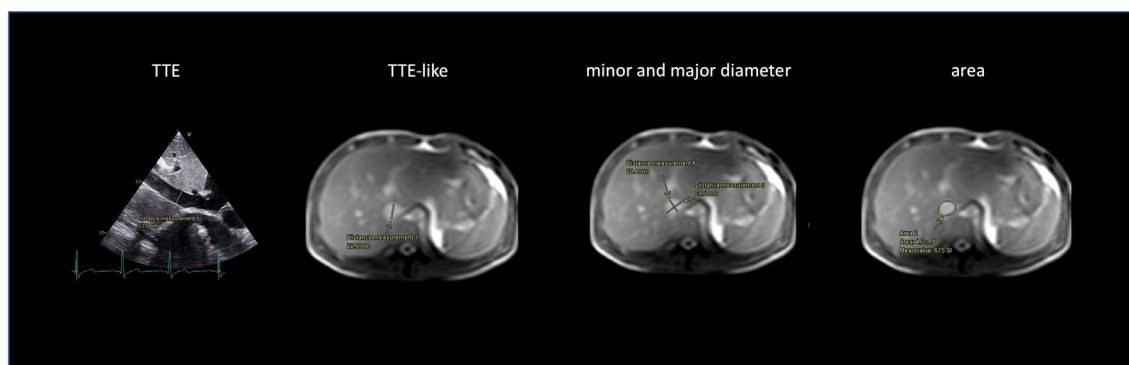
FIGURE 2: Comparison of IVC measurements. On the left is shown the expiratory IVC at TTE in longitudinal direction. The IVC diameter at TTE was measured 1–2 cm below the confluence with the hepatic veins (left). For analysis of the IVC at MRI, we used different strategies, i.e., using a TTE-like orientation (middle left), measuring the minor and major IVC diameters (middle right), and contouring the IVC area (right). Measurements were performed at expiration and inspiration.

FIGURE 3: Change in orientation of the major diameter of the IVC between inspiration and expiration. The major diameter is indicated by the yellow line at end expiration (panel **a**), halfway inspiration (panel **b**), and end inspiration (panel **c**).
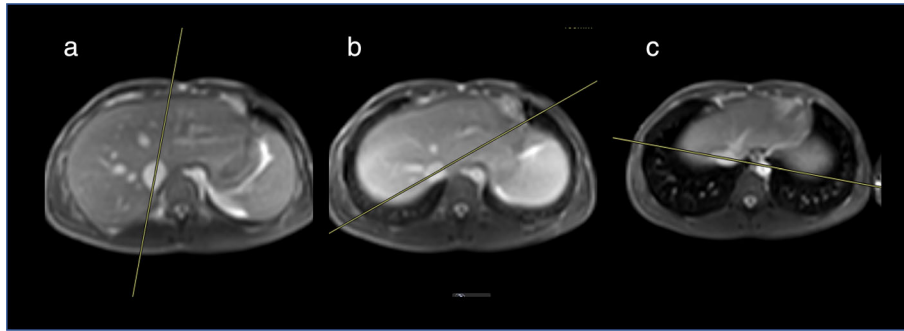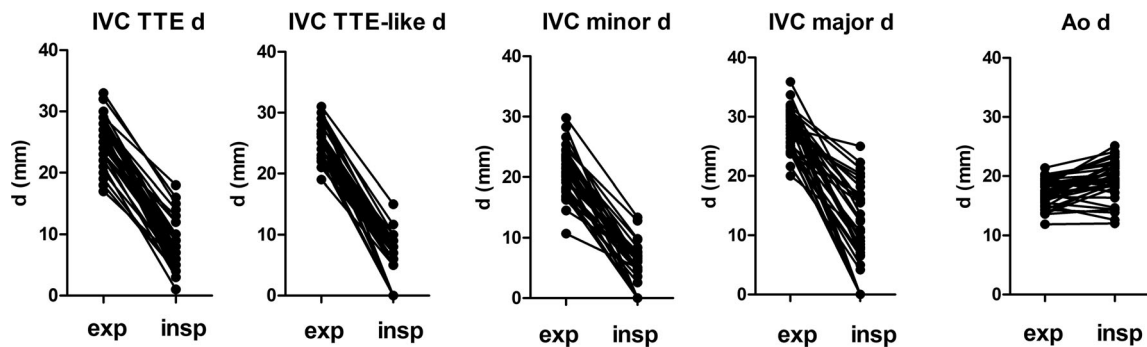

FIGURE 4: Changes in IVC diameter between expiration and inspiration at TTE and at MRI using the differences approaches as explained in Fig. 2. Abbreviations: d, diameter; insp, inspiration; exp, expiration.

period of at least 2 weeks between readings and by a second reader blinded to the results of the first reading/first reader.

Statistical Analysis

All statistical tests were performed using GraphPad (version 5.04) or Rstudio (version 2023.03.1, Posit Software). First, an outlier test was applied to the diameter results (Grubbs test, alpha 0.05). Next, a D'Agostino and Pearson omnibus test confirmed the normal distribution of all CI and expiration measures. A repeated measures ANOVA test with Bonferroni correction was used to evaluate the differences between TTE and MRI measurements of the IVC. Finally, Bland–Altman plots were obtained to assess the agreement between diameter measurements at MRI and TTE. A P value <0.05 was considered statistically significant. Intrareader and inter-reader agreement of the expiratory IVC diameter/area and CI were assessed by using intraclass correlation coefficients (ICCs, −2-way model, absolute agreement) and Bland–Altman analysis with 95% limits of agreement. ICCs below 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and above 0.9 were defined as poor, moderate, good, and excellent, respectively.[22]

Results

The study cohort included 38 male elite cyclists (mean age 26 ± 4 years). All subjects successfully completed the TTE and MRI exam. Because of an outlier, one subject was excluded from the analysis, yielding a total of 37 subjects. At
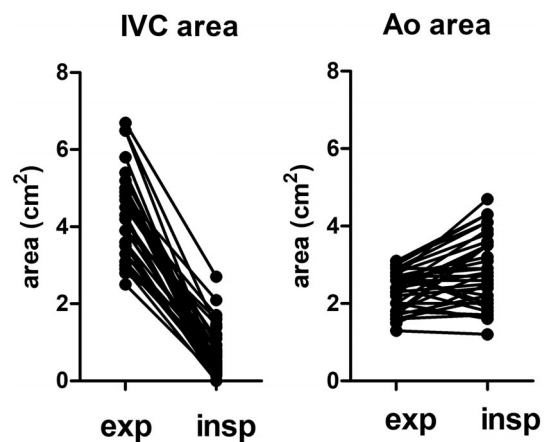
FIGURE 5: Changes in IVC and aortic area between expiration and inspiration. The aortic area was measured at the same position and same time frame as the IVC measurement both at expiration and inspiration.

TTE, the expiratory and inspiratory IVC diameter were 25 ± 4 mm (range 17–33 mm) and 8 ± 4 mm (range 1–18 mm) respectively, yielding a CI of 66 ± 14% (range 38%–95%). At MRI, the expiratory IVC diameter was 25 ± 3 mm (range 19–31 mm) using a TTE-like diameter orientation, and the major and minor diameters were 28 ± 4 mm and 21 ± 4 mm, respectively (Fig. 4). Collapsibility indices were 76% ± 14%, 63% ± 27%, and 75% ±

FIGURE 6: Expiratory and inspiratory IVC at MRI and TTE in three subjects. In each case, CI for each modality is provided. For MRI, the TTE-like diameter for CI calculation was used.

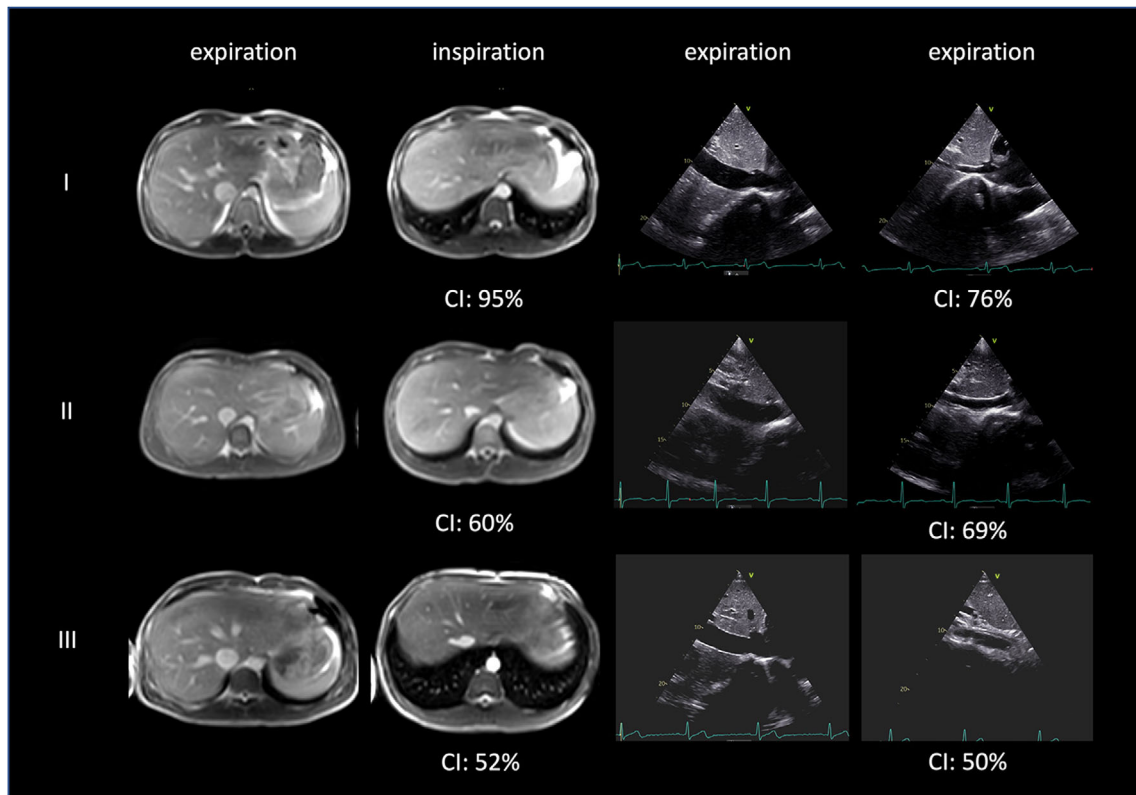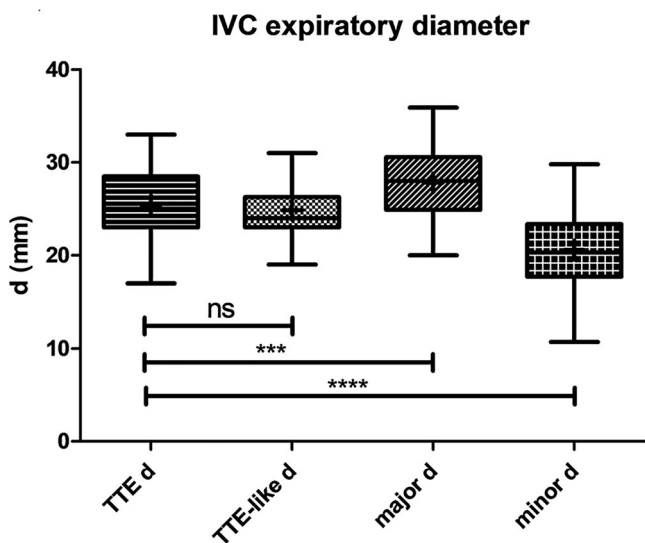FIGURE 7: Comparison of IVC expiratory diameter between TTE and MRI. While no significant differences were found between TTE and the TTE-like approach at MRI, significant differences were found between TTE and MRI measurements of minor and major diameters. *$P < 0.05$. Bold line: median; "+": mean; box = 25/75%; whiskers = min/max. ns, not significant, i.e., P value 0.242.
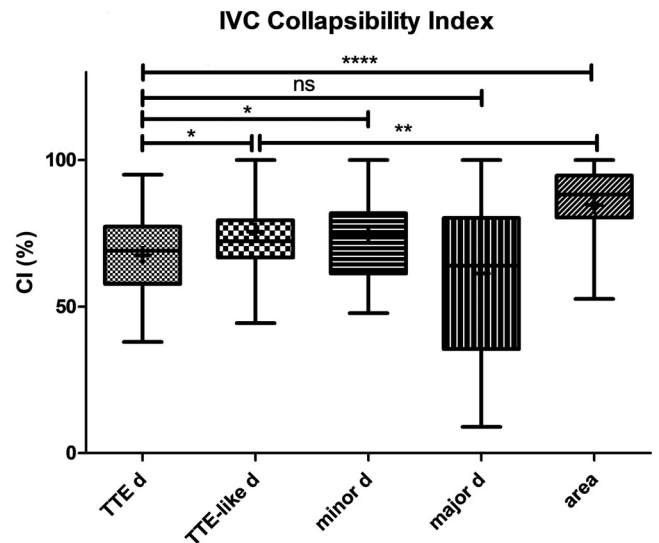
FIGURE 8: Comparison of CI between TTE and MRI. Significant differences were found between TTE and MRI approaches. Moreover, IVC area yielded significantly higher CI values than using a TTE-like diameter-based approach. *$P < 0.05$. Bold line: median; "+": mean; box = 25/75%; whiskers = min/max. ns, not significant, i.e., P-value 0.277.

16%, respectively. The major diameter of the IVC reorientated between expiration and inspiration, with a mean angulation of 41% ± 16% but with a very wide range (12%–81%) between subjects (Fig. 3 and Video S2). The expiratory

IVC area was 4.3 ± 1.1 cm^2 and yielded a CI of 86% ± 14% (Fig. 4). During inspiration, the pattern of IVC collapse was flattened in 27 subjects and circular in 10 subjects. Eight participants (22%) showed no discernible IVC cavity at

TABLE 1. Intrareader and Inter-reader Agreement

	Intrareader	Inter-reader
ICC EXP		
TTE-like	0.760	0.771
	(0.583–0.868)	(0.601–0.875)
Minor d	0.803	0.631
	(0.65–0.894)	(−0.043–0.863)
Area	0.839	0.822
	(0.710–0.913)	(0.681–0.904)
TTE	0.634	0.596
	(0.396–0.793)	(0.298–0.779)
ICC CI		
TTE-like	0.713	0.593
	(0.512–0.840)	(0.341–0.766)
Minor d	0.744	0.546
	(0.556–0.859)	(0.280–0.736)
Area	0.841	0.833
	(0.713–0.915)	(0.664–0.916)
TTE	0.704	0.545
	(0.439–0.847)	(0.148–0.766)

CI, collapsibility index; d, diameter; EXP, expiratory IVC size; ICC, intraclass correlation coefficient.

inspiration suggesting complete (or near-complete) collapse at MRI. All subjects showed a CI value >50% at MRI compared to 35/37 subjects (94%) at TTE. The expiratory aorta had a diameter of 17 ± 2 mm and an area of 2.3 ± 0.5 cm^2, the inspiratory aorta was 19 ± 3 mm and had an area of 2.9 ± 0.9 cm^2 (Figs. 4 and 5). The expiratory IVC to aortic area ratio was 1.9 ± 0.7. Figure 6 shows the expiratory and inspiratory IVC at MRI and TTE in three subjects as well as the CI values. The online videos allow better appreciation of the appearance of the IVC and respiratory changes over the respiratory cycle at TTE (Video S1) and MRI (Video S2).

Using a TTE-like approach no significant differences were found in expiratory IVC diameter measurement ($P = 0.242$), however, MRI yielded significantly higher CI values than TTE (Figs. 7 and 8). Moreover, CI values obtained by IVC area yielded not only significantly higher values than TTE, but also than the TTE-like MRI approach. In the supplementary figure are shown the Bland–Altman plots of the relation between expiratory IVC diameter measurements at TTE and MRI.

Intrareader and inter-reader agreement for measurement of expiratory IVC size and CI were moderate for TTE (i.e., 0.545–0.704) and moderate to good for MRI (i.e., 0.546–0.841; see Table 1 and Figs. S2 and S3 in the Supplemental Material). Remarkably, using area rather than diameter to assess the respirophasic variation of the IVC yielded the highest ICC values (i.e., 0.822–0.841).

Discussion

This proof-of-concept study reports the respirophasic variation of the IVC by means of real-time cine MRI. The study population consisted of a healthy group of male elite cyclists and MRI findings were compared to the TTE approach as recommended by the ASE/EACVI. Using two transverse slices through the upper part of the liver, expiratory IVC size and inspiratory collapse could be assessed in all subjects. MRI yielded similar expiratory IVC diameters as TTE, and significantly higher inspiratory collapsibility indices. Using a CI cut-off of more than 50%, excellent agreement was found between modalities. As the expiratory IVC has an oval or elliptical shape, and moreover shows an inspiratory reshaping with re-orientation of the major IVC diameter, assessment of IVC area rather than diameter may be a better alternative to evaluate IVC size and collapsibility. Moreover, IVC area assessment showed the highest ICC values for intra-reader and inter-reader agreement. As this real-time cine acquisition takes only 15 sec, it has potential to be easily integrated into a routine MRI protocol and could provide valuable information about the presence of increased right heart filling pressures in patients undergoing an MRI exam.

The assessment of CVP is important in many cardiac diseases.[1–5] This is part of a standard TTE exam, and the ASE/EACVI guideline recommend evaluating the IVC in longitudinal direction using a subcostal view.[10] Assessment of IVC collapsibility is performed during inspiration or, preferably, using a sniff-test. The optimal region for IVC evaluation is set 1–2 cm distally to the entrance of the hepatic veins into the IVC. Although a longitudinal view is the least affected by the craniocaudal movement of the diaphragm during the respiratory cycle, there is always a risk of off-axis measurement yielding incorrect assessment of IVC diameters and collapsibility indices.[6,18] Moreover, as confirmed by our study results, the expiratory IVC, in non-pathological conditions, has an oval/elliptical rather than a circular shape.[6,19] Use of a one-dimensional measurement, i.e., distance, is thus dependent on the orientation in which the IVC is transected. In addition, we found an inspiratory reshaping of the IVC, with not only a flattening but also a rotation of the major diameter from a posterolateral orientation toward a more anterolateral orientation. The magnitude of this reshaping, however, was highly variable among participants. These findings favor a cross-sectional, i.e., a transverse view cutting the IVC in

perpendicular direction, rather than a longitudinal view as recommended by the ASE/EACVI guideline.[6,10,20,21] Moreover, this has the advantage of allowing a two-dimensional, i.e., area, measurement.[6,20,21] Another reason to use a transverse rather than a longitudinal view at MRI, is that at echocardiography, the operator can reposition the probe while scanning to correct for respiratory-induced motion in the mediolateral direction, while MRI lacks this possibility. A final advantage of transverse slice orientation is that not only the IVC but also the abdominal aorta is visualized, allowing appreciation of both vessels in relation to each other (eg, by defining IVC/aortic area ratios). The downside of a transverse slice orientation is that it suffers from through-plane motion due to the craniocaudal motion of the diaphragm. To overcome this limitation, we used two slices, rather than one slice, with a slice separation equaling the typical through-plane motion. Positioning the upper slice just below the confluence of the hepatic veins with the IVC on an expiratory coronal scout view assured a good coverage of the upper intrahepatic part of the IVC over the respiratory cycle. Moreover, IVC caliber changes can be related to the respiratory motion as reflected by the movement of the thoracic cage.

Expiratory IVC diameters using a TTE-like approach matched well between imaging modalities. However, MRI yielded slightly but significantly higher CI values than TTE. Possible explanations for the difference in CI may be related to differences in spatial/temporal resolution, differences in inspiratory depth between imaging modalities or the different approach used to study the IVC, i.e., longitudinal (TTE) versus cross-sectional (MRI). The findings, however, are reassuring because they imply that the risk of false negative findings at MRI is low. Finally, as discussed above, use of an area rather than a diameter may be a better approach to evaluate IVC size. In our study IVC area yielded significantly higher CI values than TTE or MRI TTE-like diameter approaches.

Limitations

Our study has several limitations. A first limitation is the relatively small study group comprising exclusively of male elite athletes instead studying of a cohort of normal, gender-matched, subjects. As it is well known that endurance exercise causes right atrial and IVC dilatation the reported IVC size and CI values cannot be used as normal reference values.[21,23] The rationale for our approach was that TTE and MRI studies could be performed consecutively, minimizing the risk of possible confounders, such as changes in fluid balance or loading conditions between cardiac exams. Based on this pilot study, in a next step the MRI approach can be applied to determine age- and gender-matched values in a normal cohort, and can be used to correlate and validate MRI findings to (semi)-invasive measures of RAP. Second, the spatial and temporal resolution of real-time cine MRI is considerably poorer than that of TTE, possibly explaining some of the

differences in study results between imaging modalities. Our sequence parameters were optimized to obtain the best trade-off in spatial and temporal resolution to image simultaneously the IVC in real-time in two slices. Despite the lower spatial resolution of MRI, real-time cine imaging allowed accurate measurement of expiratory IVC caliber and assessment of inspiratory collapse with good to excellent ICC values, not inferior to TTE. A third point of critic is the use of two slices with arbitrary choice of slice distance, set at a fixed distance of 30 mm deemed to represent the total respiratory excursion. Future use of a navigator to monitor and track the diaphragmatic excursion may be appealing as respiratory-corrected IVC slice tracking approach. A fourth point of critic is the difference in slice direction, i.e., longitudinal versus cross-sectional between imaging modalities, which might explain some of the reported differences. A final limitation is that TTE and MRI studies were performed during free breathing. Although the ASE/EACVI recommends a brief sniff as inspiration may not elicit an inspiratory response, the MRI-based CI values exceeded 50% in all subjects, considered as cut-off value (CI > 50%) for sniff-based CI approach.

Conclusions

This pilot study presents a novel, fast and noninvasive approach to quantify the respirophasic variation of the IVC by means of real-time cine MRI. Integrating this sequence into a routine imaging protocol may increase the potential of MRI to more comprehensively study cardiac patients.

Appendix A

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