Cardiovascular Mechanisms of Extravascular Lung Water Accumulation in Divers

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This study assessed the relation between altered cardiac function and the development of interstitial pulmonary edema in scuba divers. Fifteen healthy men performed a 30-minute scuba dive in open sea. They were instructed to fin for 30 minutes and were wearing wet suits. Before and immediately after immersion, cardiac indexes and extravascular lung water were measured using echocardiography and lung ultrasound, respectively. The mean ultrasound lung comet score increased from 0 to 4.6 ± 3.4. The diameter of the inferior caval vein increased by 47 ± 5.2%, systolic pulmonary artery pressure by 105 ± 8.6%, left atrial volume by 18.0 ± 3.3%, and left ventricle end-diastolic volume by 10 ± 2.4% suggesting that both right and left ventricular (LV) filling pressures were elevated. Doppler studies showed an increased mitral E peak (+2.5 ± 0.3%) and E/A ratio (+22.5 ± 3.4%) with a decreased mitral A peak (−16.4 ± 2.7%), E peak deceleration time (−14.5 ± 2.4%) consistent with rapid early LV filling but without a change in LV stroke volume. There was an increase in right/left ventricle diameter ratio (+33.6 ± 4.8%) suggesting a relative increase in right-sided heart output compared with the left. Furthermore, the lung comet score correlated significantly with inferior caval vein diameter, systolic pulmonary artery pressure, right/left ventricle diameter ratio, and E-wave deceleration time. In conclusion, the altered right/left heart stroke volume balance could play an essential role in the development of immersion pulmonary edema. Our findings have important implications for the pathogenesis of cardiogenic pulmonary edema. **(Am J Cardiol 2017;■:■−■)**

Background

A recent review in this journal outlined the pivotal role of the right ventricle in the pathogenesis of acute pulmonary edema.[1] The objective of our study was to investigate the pathophysiological mechanisms contributing to immersion induced pulmonary edema during a scuba dive. We assessed the changes in cardiac preload, right, and left ventricular (LV) function and determining the correlation between changes in cardiovascular physiology and the accumulation of extravascular lung water.

Methods

Fifteen professional male scuba divers were recruited. All volunteers were healthy, nonsmokers, and had no history of cardiovascular or pulmonary disease. Each gave written informed consent for participation in this study. All experimental procedures were conducted in line with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee (Comité de Protection des Personnes-CPP Sud Mediterranée V, ref 1128). The methods and potential risks were explained to participants in detail before starting experiments.

Divers performed a sea dive at shallow depth (6 to 8 m of seawater), and the divers wore 7-mm neoprene wet suits. They were instructed to fin for 30 minutes and to cover 900 m. The breathing gas was air, and divers used open-circuit breathing apparatus (Legend; Aqua Lung, Carros, France). Before and immediately after immersion, cardiac indexes and extravascular lung water (EVLW) were assessed using echocardiography and lung ultrasound, respectively.

Ultrasonographic examinations were performed by an experienced sonographer using a commercially available ultrasound system (Vivid I; GE Medical, Horten, Norway) with a 1.5- to 4-MHz phased array transducer. Images were analyzed in line with the American Society of Echocardiography guidelines[2] (see details in Supplementary Data). The presence of EVLW was assessed using lung ultrasound by counting the number of B-lines or ultrasound lung comets (ULCs).[3]

Data were statistically analyzed using the Prism 6 software (GraphPad Software, La Jolla, California). Each subject served as his own control. Data distribution was assessed using a Kolmogorov-Smirnov test. Normally distributed values recorded at 2 different times were compared using the

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Student *t* test for paired data; Wilcoxon's paired signed rank test was used for non-normally distributed data. Correlations between ULC score and cardiovascular parameters were assessed using the Pearson's test. Differences between groups were considered statistically significant at $p < 0.05$. All values are expressed as mean ± SD.

Results

All subjects performed the protocol without clinical features of pulmonary edema or other complications. Their age was (mean ± SD) 33.2 ± 11.3 years old; height, 1.78 ± 0.18 m; and body weight, 71.2 ± 8.3 kg. The mean water temperature was 14.6 ± 0.8°C. No ULCs were detected, and all the cardiac parameters were normal before the dives. ULCs were detected in 73.3% divers after the dive. A significant increase in inferior caval vein diameter and cross-sectional area, volume of the right atrium, right ventricular (RV) end-diastolic area, RV fractional area change, and systolic pulmonary artery pressure was observed.

An increase in the cross-sectional area and volume of the left atrium and LV end-diastolic volume and area was demonstrated. There was no significant change in the LV ejection fraction (EF), end-systolic area, end-systolic volume, or stroke volume. The RV/LV area ratio, however, increased significantly by 60%, suggesting an important increase in RV stroke volume compared with LV stroke volume.

Our data also revealed that the mitral E peak increased and the A peak significantly decreased after dive. The E/A ratio increased after the dive, and the E-wave deceleration time shortened significantly after diving compared with basal levels (Table 1).

The Figure 1 shows ULC score correlated significantly with the percent changes in inferior vena cava diameter ($p = 0.005$), and the systolic arterial pulmonary pressure (ΔsPAP) ($p = 0.011$), ΔRV/LV ($p = 0.002$), and variation of E peak deceleration time (early left ventricular filling deceleration time, ΔEDT) values ($p = 0.007$).

Discussion

The principle finding of this study was that a 30-minute open sea scuba dive resulted in increased heart preload, changes in LV filling flow, increased RV area change with EVLW accumulation in 73% of divers. To our knowledge, this is the first study to show the changes in RV physiology correlated with the development of interstitial pulmonary edema.

Our findings show that scuba air diving results in increased right-sided cardiac preload and generation of higher pulmonary artery pressures. We demonstrated an increased RV size and fractional area change suggesting a significant increase in RV stroke volume. The changes observed in the right-sided cardiac are associated with an increase in left heart preload but, interestingly, without a corresponding increase in LVEF and stroke volume (SV). Note that the cardiac output was significantly greater after diving secondary to the high heart rate induced by the finning effort.

Our results also revealed changes in LV filling pattern after diving. We observed an increase in E wave (2%) and E/A ratio (22%), whereas the A wave and EDT decreased by 16% and 14%, respectively. Marabotti et al[4] observed similar changes in mitral Doppler flow. These indexes are widely used for clinical characterization of LV "diastolic function" and are linked with delayed ventricular relaxation (observed in early hypertensive heart disease or with aging) or with increased wall stiffness (observed in advanced hypertensive heart disease or in constrictive/restrictive heart disease).[5] However, in the context of normal hearts, the changes probably reflect rapid early filling driven by the higher pulmonary artery pressures and secondary to increased work done by the right ventricle.[6] It is unlikely our subjects had reduced LV compliance (in the absence of known heart disease or hypertension) although it is plausible that the subjects reached the LV/pericardial elastic limit toward the end of diastole or had abnormal intracellular calcium homeostasis.[7]

We suggest that the changes in LV filling patterns could be the result of an increased pulmonary venous pressure causing a rapid early diastolic filling due to the higher initial atrioventricular pressure gradient. The reduced A-wave velocity is a consequence of the higher end-diastolic pressure as the LV is already well filled. The "blood shift" induced by immersion will, sequentially, increases the RV filling pressure, increasing RV Frank-Starling mechanism, RV contraction, pulmonary artery pressure, capillary pressure and, finally, LV filling pressure.[6] At the same time, dilatation of the right-sided cardiac might hamper filling of the left ventricle (ventricular interdependence) because of the limited distensibility of the pericardium and, so, may inhibit LV stroke volume. Our results support the hypothesis of an RVSV/LVSV mismatch as the principle cause of acute pulmonary edema in divers.[1]

The major result presented in this study is the statistically significant correlation between the number of ULC and changes in the cardiovascular indexes. Thus, accumulation of EVLW was associated with increased systolic arterial pulmonary pressure and inferior vena cava diameter (both markers of increased right-sided cardiac preload) and reduced EDT and an increased RV/LV ratio indicating that a scuba dive causes an imbalance between right and left cardiac "function" which results in the accumulation of EVLW.

Recently, a review in this journal suggested acute pulmonary (alveolar) edema resulted from a mismatch or imbalance between the right and LV SVs.[1] Although the pathophysiology of acute pulmonary edema is generally described in terms of a failing left ventricle, for acute pulmonary edema to occur, there must be a mismatch between the right and LV SVs as fluid is lost from the circulation into the airspaces. The augmentation of RV contractility increases RV stroke volume (and pulmonary pressures) relative to LVSV which could then cause an increase in capillary hydrostatic pressure leading to transudation of fluid into the lung interstitium.[1]

We propose that during scuba air dive, with medium-intensity finning exercise in healthy divers, pulmonary capillary hydrostatic pressure increases because of an augmented RV SV that exceeds the LV SV. A sustained difference in ventricular SVs will cause overloading of the lymphatic system during exertion, triggering EVLW accumulation. This mechanism also explains why divers with cardiovascular disease, such as hypertension, are at

Table 1
Right- and left-sided cardiac function parameters measured before and immediately after performing the dive (n = 15)

Cardiac indices	Pre-dive	Post-dive	Change (%)
Right heart			
Inferior caval vein diameter (cm)	1.7 ± 0.3	2.5 ± 0.5*	*47*± 5.2
Inferior caval vein area (cm^2)	2.3 ± 0.2	4.8 ± 0.3*	115 ± 12
Right atrial volume (mL)	35 ± 4.2	52 ± 6.5*	*50* ± 3.8
Right atrial area (cm^2)	13 ± 2.1	18 ± 1.5*	*47* ± 3.5
Right ventricle end-diastolic area (cm^2)	18 ± 1.1	25 ± 1.8*	*36* ± 4.5
Right ventricle end-systolic area (cm^2)	12 ± 2.3	12 ± 2.4	*0.8* ± 0.1
Right ventricle fractional area change (%)	33 ± 3.5	51 ± 4.5*	*53* ± 6.2
Right ventricle end-diastolic diameter (mm)	25 ± 2.8	27 ± 3.2	*5.2* ± 0.7
Right ventricle end-systolic diameter (mm)	18 ± 2.2	19 ± 1.8	*3.8* ± 0.2
Systolic pulmonary arterial pressure (mmHg)	7.2 ± 0.9	15 ± 2.1*	*106* ± 8.6
Left heart			
Left atrial area (cm^2)	14 ± 2.7	15 ± 2.7*	*9.6* ± 1.5
Left atrial volume (mL)	36 ± 4.2	43 ± 6.2*	*18* ± 3.3
Left ventricle end-diastolic area (cm^2)	33 ± 4.2	34 ± 4.6*	*2.1* ± 0.2
Left ventricle end-systolic area (cm^2)	18 ± 2.5	18 ± 2.5	*-0.5* ± 0.05
Left ventricle fractional area change (%)	45 ± 2.1	45 ± 2.1	3.5 ± 0.3
Left ventricular end-systolic volume (mL)	120 ± 15.8	125 ± 13.5	*3.9* ± 0.6
Left ventricular end-diastolic volume (mL)	44 ± 5.4	48 ± 5.2*	*10* ± 2.4
Left ventricular ejection fraction (%)	64 ± 7.5	62 ± 5.8	*-3.4* ± 0.2
Stroke volume (mL)	77 ± 6.8	77 ± 6.9	*0.4* ± 0.0
Heart rate (bpm)	63 ± 8.4	82 ± 7.3*	*31* ± 5.1
Cardiac output ($L.min^{-1}$)	4.8 ± 0.8	6.3 ± 0.5*	*32* ± 4.2
Peak E wave velocity ($m.s^{-1}$)	0.81 ± 0.2	0.83 ± 0.0*	*2.5* ± 0.3
Peak A wave velocity ($m.s^{-1}$)	0.55 ± 0.12	0.46 ± 0.09*	*-16.4* ± 2.7
E wave deceleration time (ms)	228 ±19.8	195 ± 24*	*-15* ± 2.4
E/A ratio	1.5 ± 0.24	1.8 ± 0.24*	*23* ± 3.4
Ratio right to left ventricles			
Ratio R to L ventricles end-diastolic area (%)	55 ± 6.4	74 ± 8.5*	*34* ± 4.8

Values recorded at before and after dive were compared using the Student *t* test for paired data. Italic values are %change indicates change from pre-dive to post-dive value.

* $p < 0.05$ versus predive.

increased risk of developing pulmonary edema because of an impaired ability to increase LVSV. We suggest that the hypothesis of a breakdown in the alveolar-capillary membrane as a dominant cause of immersion pulmonary edema is unlikely because of the rapid recovery of most subjects. Our findings are consistent with previous reports of a higher incidence of immersion pulmonary edema in cold water (due to systemic vasoconstriction) and hypertension (causing a greater peripheral vascular resistance) limiting left but not RV stroke volume. A higher systemic vascular resistance, furthermore, might also occur from an elevated hydrostatic pressure through limb compression secondary to immersion. Higher heart rates will exacerbate the difference in RVSV and LVSV resulting in lymphatic drainage overflow and acute pulmonary edema.[1]

Although this was a small study with 15 subjects, it was sufficient to demonstrate statistically significant results. We did not assess the effects in any female divers, and the study was not blinded to participants or the ultrasonographer. The data, however, were analyzed by an independent researcher. We were only able to assess the cardiovascular changes immediately after swimming and may, therefore, have underestimated the physiological changes. We did not assess work of breathing despite its known affects cardiovascular mechanics. During scuba diving, negative static lung load is strongly negative in many situations, which could promote the occurrence of pulmonary edema. Further study will be necessary to confirm any specific role of static lung load and work of breathing in the physiological mechanisms leading to immersion pulmonary edema. In addition, the cardiovascular changes observed in this study will trigger release of hormones, such as atrial natriuretic peptide, which act directly on capillary permeability[8] and the pulmonary lymphatic system's drainage capacity.[9] The role these hormones play in the onset of immersion pulmonary edema will need to be analyzed in future studies.

RV fractional area change was used rather than EF; however, this is a reasonable surrogate.[10] We did not assess for the presence of a patent foramen ovale in our subjects. The presence of a patent foramen ovale may, theoretically, lessen the risks of pulmonary edema by offloading the left atrial pressures into the right atrium. Our findings however would suggest a greater right-sided cardiac volume in the presence of higher lung comet scores suggesting that left to right atrial shunting is unlikely to be an important protective mechanism.

Our results showed that 30 minutes finning during scuba air dive at shallow depths induced interstitial pulmonary edema (defined by the lung comet score) in 73% of participants. The severity of lung comet score was significantly correlated with measurements of increased cardiac preload, RV area change (a surrogate of RVEF), and pulmonary

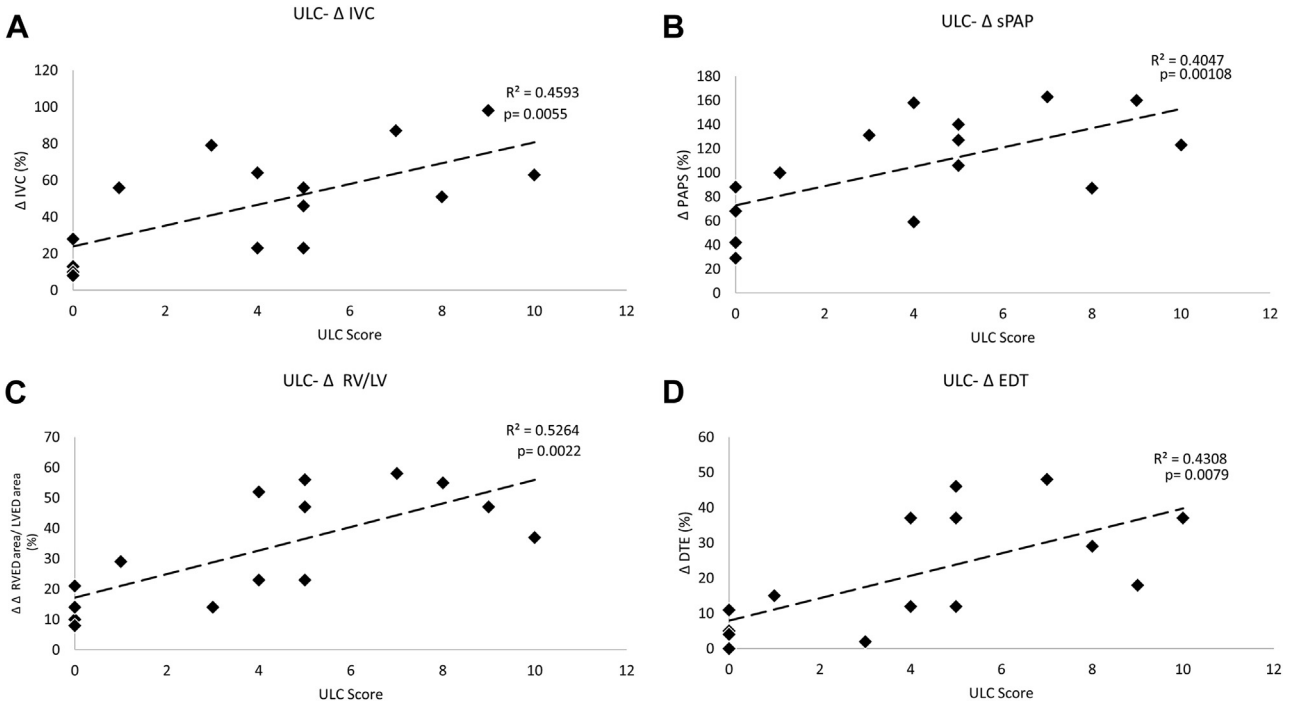

Figure 1. Ultrasound lung comet score correlates with changes to various heart parameters: *(A)* inferior caval vein/inferior vena cava (ΔIVC), *(B)* systolic arterial pulmonary pressure (ΔsPAP), *(C)* change in cross-sectional RV area/LV areas ratio (ΔRV area/LV area), and *(D)* early left ventricular filling flow deceleration time (ΔEDT). Values are expressed as percentages compared with the resting value recorded before dive.

artery pressure but not LVEF or LVSV. We suggest that the imbalance between right and left heart stroke volumes is central to the development of immersion pulmonary edema. A greater understanding of the mechanism of immersion pulmonary edema has important implications for the prevention of a potentially catastrophic condition. Our findings, furthermore, may help to explain the development of acute pulmonary edema in cardiac diseases such as acute myocardial infarction where RV "function" is preserved.[11] In hypertensive heart disease, there may be a similar mismatch in stroke volumes predisposing to pulmonary edema.[12,13] The development of increased pulmonary hydrostatic pressure is a consequence of increased RV work combined with the absence of a sufficient increase in LV stroke volume.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.11.050.

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