Cardiovascular response to acute hypoxemia induced by prolonged breath holding in air

Alessandro Pingitore,1 Angelo Gemignani,2 Danilo Menicucci,2 Gianluca Di Bella,3 Daniele De Marchi,1 Mirko Passera,1 Remo Bedini,1 Brunello Ghelarducci,2 and Antonio L’Abbate4

1Consiglio Nazionale delle Ricerche Institute of Clinical Physiology, Pisa; 2Department of Human Physiology, University of Pisa, Pisa; 3Cardiovascular Department, University of Messina, Messina; and 4Scuola Superiore Sant’Anna, Pisa, Italy

Submitted 24 May 2007; accepted in final form 7 November 2007

Pingitore A, Gemignani A, Menicucci D, Di Bella G, De Marchi D, Passera M, Bedini R, Ghelarducci B, L’Abbate A. Cardiovascular response to acute hypoxemia induced by prolonged breath hold in air. Am J Physiol Heart Circ Physiol 294: H449–H455, 2008. First published November 9, 2007; doi:10.1152/ajpheart.00607.2007.—Prolonged breath hold (BH) represents a valid model for studying the cardiac adaptation to acute hypoxemia in humans. Cardiac magnetic resonance (CMR) allows a three-dimensional, high-resolution, noninvasive, and nonionizing anatomical and functional evaluation of the heart. The aim of the study was to assess the adaptation of the cardiovascular system to prolonged BH in air. Ten male volunteer diving athletes (age 30 ± 6 yr) were studied during maximal BH duration with CMR. Four epochs were studied: I, rest; II and III, intermediate BH; and IV, peak BH. Oxygen saturation (SO2), heart rate (HR), blood pressure (BP), systemic vascular resistance (VR), end-diastolic (EDV) and end-systolic volumes (ESV), stroke volume (SV), cardiac output (CO), ejection fraction (EF), maximal elastance (EL), stroke volume, systolic wall thickness (SWT), and end-systolic wall stress (ESWS) of the left ventricle (LV) were measured in all four BH epochs. Average BH duration was 3.7 ± 0.3 min. SO2 was reduced (I: 97 ± 0.2%, range 96–98%, vs. IV: 84 ± 2.0%, range 76–92%; P < 0.00001). BP, EDV, ESV, SV, CO, and ESWS linearly increased from epochs I to IV, whereas EF, EL, and SWT showed an opposite behavior, decreasing from resting to epoch IV (all trends are P < 0.01). During prolonged BH in air, a marked enlargement of the LV chamber occurs in healthy diving athletes. This response to acute hypoxemia allows SV, CO, and arterial pressure to be maintained despite the severe reduction in LV contractile function.

Diving athletes; apnea; cardiovascular system; cardiac magnetic resonance imaging

Studies performed in animals in hypoxemic conditions have shown significant changes in cardiovascular parameters. For instance, airway obstruction in sleeping dogs was associated with increased mean blood pressure (24), and periodic aperiodic in air in sedated pigs were associated with increased left ventricular (LV) end-diastolic pressure and lengthening of end-diastolic and end-systolic myocardial fibers (3). The latter changes were coupled to reduction in heart rate, stroke volume, and cardiac output (3). In a rat model of asphyxial cardiac arrest, the increase in LV end-diastolic dimension was positively correlated with asphyxia duration (23). In humans, a suitable model for studying cardiac response to acute hypoxemia is spontaneous prolonged breath hold (BH) in healthy subjects (1, 7, 20). Diving athletes are used to the practice of sport apnea and can sustain sufficiently long BH, suited to the timing of more advanced cardiac imaging, in the absence of any concomitant disease potentially interfering with the cardiac response to hypoxemia.

Cardiovascular response to BH in diving athletes has been studied in different experimental conditions, i.e., extreme or shallow diving depth, hyperbaric chamber, and during face immersion after submaximal exercise (2, 8, 9, 10, 30). The typical response, that is, peripheral vasoconstriction and bradycardia, corresponds to the so-called diving reflex (1, 7, 20). However, the cardiovascular response to maximal prolonged BH at inspiration in normobaric condition and without the interference of the diving reflex still has not been assessed.

Cardiac magnetic resonance (CMR) allows a three-dimensional, high-resolution, noninvasive, and nonionizing anatomical and functional visualization of the heart. It represents the gold standard for quantitative evaluation of the cardiac volumes and of the LV global and regional function (26, 27). The aim of this CMR study was to assess the homeostatic response of the cardiovascular system to acute hypoxemia in healthy diving athletes during BH in air. Our experimental approach provided information on the time course of hemodynamic changes as well as morphological and functional modifications of the LV in extreme physiological conditions without the interference of the diving reflex that occurs during diving.

Methods

Subjects. Ten male diving athletes (mean age 30 ± 6 yr) were studied with CMR at rest and during prolonged BH in air. All volunteers gave their informed consent to take part in the study. The protocol was approved by the Local Ethical Committee.

Breath hold study. For each athlete, BH was performed in maximal inspiration. The BH mean duration depended on the subjective capacity to maintain this condition, and it was verified in a separate session outside the MR scanner, during which two BH sessions were performed (BH1 = mean 3.6 ± 0.2 min; BH2 = mean 3.8 ± 0.1). Based on the BH mean duration of each athlete, we designed a personalized timing for the CMR acquisition. To dynamically identify the cardiovascular effects of apnea, we divided each experimental CMR session into four epochs: I, resting condition; II and III, intermediate BH; and IV, BH peak. For each epoch, a MR acquisition was performed. The intermediate epochs II and III were calculated for each athlete according to the maximum BH time. In this way, the four epochs were equally spaced during the apnea period in all the athletes.

During CMR sessions, values from four BH sessions were obtained for each athlete: the first two were short and lasted the time necessary to acquire LV sequences in longitudinal and parasagittal views. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: A. Pingitore, CNR Institute of Clinical Physiology, Pisa, Via Moruzzi 1, 56124 Pisa, Italy (e-mail: pingi@ific.cnr.it).

http://www.ajpheart.org 0363-6135/08 $8.00 Copyright © 2008 the American Physiological Society H449
average time of these two BH sessions was 9 ± 3 s. The images obtained were used to assess resting LV parameters corresponding to epoch I. The remaining two BH sessions were maximal and were preceded by the preparation phase with which each athlete was familiarized. The first maximal BH was used for the LV longitudinal and horizontal slice acquisition and the latter for LV parasagittal slice acquisition. The two BH sessions were similar in terms of duration (intra-athlete variation of 2%) as well as heart rate (HR; 5%) and blood pressure response (5%). Also, the low limit of O2 saturation (SO2) was similar in the two maximal BH sessions in each athlete (5%). During these 2 BH sessions, the acquired images were used to assess LV parameters corresponding to epochs II, III, and IV.

**Hemodynamic parameters.** For ECG recording, three diamagnetic Red Dot disposable electrodes were placed according to DII lead, and blood pressure and SO2 were monitored continuously using a pulse oximeter for MR. The respirogram was recorded to control BH conditions.

From the above signals, five hemodynamic parameters were obtained: HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and SO2. SBP and DBP were measured noninvasively with a sphygmomanometer. MBP was calculated as follows: SBP/3 + (1/2 × DBP)/3. Hemodynamic parameters of epoch I were obtained during the short BH sessions used for the CMR acquisition of resting LV parameters. In this way, resting hemodynamic and CMR parameters were acquired simultaneously. For safety reasons, vital signs of the subjects were continuously monitored during BH in the MR scanner, and according to the study protocol, 75% was the lower limit allowed for SO2.

**Cardiac magnetic resonance.** CMR was performed on a whole body MR scanner (Signa Cvi; GE Healthcare Systems, Milwaukee, WI), operating at 1.5 T using a dedicated cardiac phased-array coil. CMR acquisition was performed according to a standardized protocol. Cine cardiac images were obtained using breath hold segmented gradient echo steady-state free precession electrocardiographic triggered sequences. Time of echo was 1.7 ms, repetition time was 4.0 ms, slice thickness was 8 mm, field of view varied from 320 to 380 mm, matrix size was 256 × 224, phase of field of view was 0.75, trigger delay was the minimum, views per segment were 8–12 according to HR, and flip angle was 45°. Two LV slices, one longitudinal and the other horizontal, were acquired, with a minimum of 30 cine frames for each slice, to calculate the LV volumes and the global indexes of LV function. A midventricular short-axis view of the LV was also acquired to measure LV diameters and calculate wall stress.

**CMR data analysis.** With the use of a commercial postprocessing program (Mass Analysis, Leiden, The Netherlands) on an independent Sun-pare Station, the endocardial borders were drawn on the two long-axis views (1 vertical and 1 horizontal) to measure the LV area and the long-axis length at end diastole and end systole. End-diastolic (EDV; ml) and end-systolic LV volumes (ESV; ml) were calculated according to the area-length method. Both EDV and ESV were used to calculate LV stroke volume (SV; ml) and ejection fraction (EF; %).

Cardiac output (CO; ml/min) was obtained as the ratio between SBP and ESV, which approximates maximal ventricular elastance (EL) (28).

**Statistical analysis.** For statistical analysis, the SPSS 11.0 package (SPSS) was used. The four surveys of each hemodynamic parameter (HR, SBP, MBP, DBP, VR, SO2) and each morphological and functional cardiac parameter (EDV, ESV, SV, CO, EF, SWT, ESWS, EL) were evaluated using the repeated-measures ANOVA model with the four level epochs (I, II, III, IV) as well as “within” factors. The “within contrast” analysis was aimed at detecting significant trends across the epochs and revealing significant variations between resting (epoch I) and the BH peak (epoch IV). These two points together constitute our follow-up analysis. Regional functional parameters of LV (SWT and ESWS) were studied using a repeated-measures ANOVA model having two within factors: the four levels of epoch factors (I, II, III, IV) and the six levels of segment factors. The levels of the segment factors were sorted according to adjacency criteria (anterior, anterolateral, inferolateral, inferior, inferoseptal, anteroseptal). For the epochs effect, the within contrast analysis was focused either to detect significant trends or reveal significant variations between resting (epoch I) and BH peak (epoch IV). For the segments effect, the detection of a significant regional trend was explored. Moreover, a different behavior among segments across epochs was investigated with the segments-epochs interaction. The significance threshold was set at P < 0.05.

**RESULTS**

All diving athletes showed good endurance to the experimental conditions, and no negative effects of prolonged BH on vital parameters were detected. For the whole sample, the mean BH duration during MR acquisition was 3.7 ± 0.3 min. All values are means ± SE.

**Hemodynamic parameters.** As indicated in Table 1, all hemodynamic parameters showed significant changes during BH, with the exception of HR (Fig. 1). SBP, DBP, and MBP linearly increased from basal condition to the BH peak (Fig. 1), while VR and SO2 showed an opposite behavior, decreasing from basal to BH peak (Fig. 1). Despite the stability of HR, all hemodynamic parameters showed significant changes between epoch I and epoch IV (Table 1). As expected, there was a drop in SO2 from 97 ± 0.2% in basal condition (range: 96–98%) to 84 ± 2% at BH peak (range: 76–92%) (P < 0.0001; Table 1).

**Volumetric and global functional parameters.** As indicated in Table 2, LV volumes and global function were significantly modified during BH. EDV, ESV, SV, and CO linearly increased from basal condition to BH peak (Fig. 2), while EF and EL showed an opposite behavior, decreasing from resting to BH peak (Fig. 2). All volumetric and global functional parameters showed significant differences between epoch I and epoch IV (Table 2).

**Regional LV function and wall stress.** As indicated in Table 3, BH induced significant changes of SWT and ESWS. Figure 3 shows diastolic and systolic changes of LV wall thickness of one of the volunteers during the four epochs of BH. Furthermore, ANOVA indicated significant interactions between LV segments and BH duration for both SWT and ESWS values. As expected at BH peak with respect to resting (Table 3), SWT decreased whereas ESWS increased.

These changes were particularly evident for anterior, lateral, and inferior LV segments (Fig. 4). On the contrary, the behavior of inferoseptal and anteroseptal segments was only slightly affected by BH (Fig. 4).
DISCUSSION

In the present study we assessed the response of the cardiovascular system to extreme acute hypoxemia induced by maximal voluntary breath hold in healthy, skilled diving athletes. Our findings showed that prolonged breath hold induced 1) a drop of \( \text{SO}_2 \) that was nominal in the first but prominent in the last breath hold period; 2) progressive dilatation of the LV cavity; 3) a significant increase in SV and CO, which occurred despite the progressive deterioration of regional and global LV systolic function; 4) a linear increase in blood pressure; and 5) different functional responses of LV segments to hypoxemia. Differently from previous studies on BH in air, we observed neither bradycardia nor increased VR or decreased CO (1, 20).

Hypoxemia and LV function. The main finding of this study was the marked enlargement of the LV in parallel with its systolic dysfunction. Despite such dysfunction and the increase in ventricular afterload (DBP), SV and CO increased. This effect may be attributed to the utilization by the LV of the preload reserve via the Frank-Starling mechanism as it occurs in the failing heart (5) or during endurance exercise in athletes (13, 16). This mechanism is particularly effective to increase

Table 1. Summary of significant effects and follow-up analyses of variance of hemodynamic parameters

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>Epoch Effect ( P ) [F(3,27)]</th>
<th>Follow Up</th>
<th>( P ) [F(1,9)]</th>
<th>Physiological Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>NS</td>
<td>Linear contrast 0.008</td>
<td>Progressive increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( I \ vs. \ IV ) 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.002</td>
<td>Linear contrast 0.001</td>
<td>Progressive increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( I \ vs. \ IV ) 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>0.00001</td>
<td>Linear contrast 0.002</td>
<td>Progressive increase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>( I \ vs. \ IV ) 0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP</td>
<td>0.00001</td>
<td>Linear contrast 0.00001</td>
<td>Progressive decrease and late abrupt drop</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quadratic contrast 0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR</td>
<td>0.03</td>
<td>NS</td>
<td>NS</td>
<td>Initial decrease and then unchanged ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( I \ vs. \ IV ) 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{SO}_2 )</td>
<td>0.00001</td>
<td>Linear contrast 0.00001</td>
<td>Progressive decrease and late abrupt drop</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quadratic contrast 0.00001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, heart rate; SBP, DBP, and MBP, systolic, diastolic, and mean blood pressures; VR, systemic vascular resistance; \( \text{SO}_2 \), oxygen saturation. \( \text{Epoch I} \), resting period; \( \text{epoch IV} \), breath hold peak.

**Fig. 1.** Changes in hemodynamic parameters. Values are means ± SE and represent heart rate (HR; bpm, beats/min), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), systemic vascular resistance (VR), and oxygen saturation (\( \text{SO}_2 \)) during resting period (\( \text{epoch I} \)), intermediate breath hold (BH; \( \text{epochs II and III} \)), and BH peak (\( \text{epoch IV} \)) in diving athletes.
CO in athletes compared with untrained individuals because of increased LV compliance that induces a greater change in SV for a given change in filling pressure (16). This mechanism leading to increased CO can also account for the lack of increased peripheral VR documented in the present study. Moreover, the formula used for calculating VR did not consider central venous pressure, which may increase during breath holding and the concomitant changes in alveolar and intrapleural pressures. However, the absence of the central venous pressure in the calculation of VR did not affect our conclusions. In fact, if central venous pressure increases during prolonged breath holding in air, VR values, calculated according to the formula VR = \frac{\text{mean arterial pressure} - \text{central venous pressure}}{\text{CO}}\), would result even lower.

Thus, in the condition of acute hypoxemia, LV preserves CO through the increase in its diastolic filling, at the expense, however, of increased LV wall stress and increased myocardial metabolic demand. The enlargement of LV has been documented in sedated pigs submitted to periodic apnea of the duration of 30 s in association with increased afterload and preload (3). In our study the enlargement of LV volumes is already evident in epoch II, when SO2 is still preserved; in this

<table>
<thead>
<tr>
<th>Volumetric and Global Functional Cardiac Parameters</th>
<th>Epoch Effect P \left[F(3,27)\right]</th>
<th>Follow-Up Analysis</th>
<th>Physiological Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV</td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>Progressive increase</td>
</tr>
<tr>
<td>ESV</td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>Progressive increase</td>
</tr>
<tr>
<td>SV</td>
<td>0.002</td>
<td>Linear contrast</td>
<td>Progressive increase</td>
</tr>
<tr>
<td>CO</td>
<td>0.001</td>
<td>Linear contrast</td>
<td>Progressive increase</td>
</tr>
<tr>
<td>EF</td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>Progressive decrease</td>
</tr>
<tr>
<td>EL</td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>Progressive decrease</td>
</tr>
</tbody>
</table>

EDV and ESV, end-diastolic and end-systolic volumes; SV, stroke volume; EF, ejection fraction; CO, cardiac output; EL, elastance values.

Fig. 2. Changes in volumetric and global functional cardiac parameters. Values are means ± SE and represent end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), cardiac output (CO), ejection fraction (EF), and maximal elastance index (EL) during resting period (epoch I), intermediate BH (epochs II and III), and BH peak (epoch IV) in diving athletes.
phase, LV enlargement can depend on the restitution of the blood volume accumulated into the central circulation during maximal inspiration. At the end of BH, when \( \text{SO}_2 \) drastically reduces, myocardial ischemia may be responsible for reduced global and regional contractility, which however does not affect SV because of the LV diastolic enlargement. Our data clearly showed both a regional and global increase in the ESWS that paralleled the regional reduction of function as assessed by systolic wall thickening. This finding is in agreement with previous data showing that the velocity of circumferential fiber shortening, an index of myocardial systolic performance, was inversely related to ESWS in a linear fashion (4). Interestingly, this negative relationship involved in particular the anterior, lateral, and inferior wall but not the interventricular septum. Unfortunately, the lack of data concerning the right ventricle did not allow us either to speculate on the right-to-left ventricle mechanical interplay or to postulate the existence of different susceptibility of LV segments to hypoxia. This represents a methodological limitation of our study. In further association with reduced regional systolic function, we observed an impairment of systolic global performance, as indicated by the reduction of maximal elastance index that paralleled the reduction in LV EF.

However, although the modifications of all the variables are more evident when \( \text{SO}_2 \) drastically drops, the cardiovascular response to breath hold, and hence the attempt to maintain homeostasis, is sustained by a combination of mechanisms that are different from the merely hypoxemic state. Accordingly, the experimental evidence that different conditions of apnea, i.e., breathing room air or pure oxygen, or even pure \( \text{O}_2 \) with

<table>
<thead>
<tr>
<th>Regional Functional Cardiac Parameters</th>
<th>Epoch Effect</th>
<th>( P )</th>
<th>Follow up</th>
<th>( P[F(1,9)] )</th>
<th>Physiological Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWT</td>
<td></td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>0.001</td>
<td>Sigmoid decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cubic contrast</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( I ) vs. IV</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Segments</td>
<td></td>
<td>0.04</td>
<td>Quadratic contrast</td>
<td>0.027</td>
<td>No changes in the interventricular septum only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWS</td>
<td></td>
<td>0.00001</td>
<td>Linear contrast</td>
<td>0.009</td>
<td>Progressive increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quadratic contrast</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( I ) vs. IV</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Segments</td>
<td></td>
<td>0.003</td>
<td>Quadratic contrast</td>
<td>0.04</td>
<td>Late increase also for interventricular septum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cubic contrast</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.04</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SWT, systolic wall thickening; ESWS, end-systolic wall stress relative values.

Fig. 3. End-diastolic and end-systolic wall thickness of left ventricle (LV) in a representative breath-holding diving athlete. Short-axis images of LV were acquired at resting (epoch I), intermediate BH (epochs II and III), and BH peak (epoch IV) after a BH lasting 4.50 min. LV wall (delimited area) shows a clear thinning from epoch I to epoch IV during both diastole (D) and systole (S). The increase of EDV and ESV at BH peak is indicated by the enlargement of end-diastolic and end-systolic LV cavity (LVC). The images also show an enlargement of the right ventricular cavity (RVC). Segments of the LV wall are depicted: An, anterior; AL, anterolateral; IL, inferolateral; In, inferior; IS, inferoseptal; AS, anteroseptal.
supplementation of 100% CO₂, increases both LV end-diastolic pressure and volume confirms that hypoxemia is an important, but not the only, mechanism responsible for the cardiovascular response to apnea (3). In fact, apnea, hypercapnia, baroreflex, and mechanoreflex mechanisms, and also the activation of the parasympathetic system, can act synergically or in opposition, on different targets of the cardiovascular system, to maintain cardiovascular homeostasis in the presence of acute hypoxemia (3, 12, 15, 17, 18, 25).

Breath hold in air and diving reflex. The results of the present study refer to a specific and well-defined condition that is maximal breath holding at maximal inspiration in a normobaric condition. This condition should be carefully distinguished from diving apnea, in which many other factors modulate the cardiovascular response. These primarily consist of the diving reflex, which induces peripheral vasoconstriction and bradycardia (6, 7, 11), and enhanced hydrostatic pressure, which affects blood volume redistribution within the vascular system. As matter of fact, changes in CO during diving apnea differ according to experimental conditions. A reduction in CO, regarded as a consequence of reflex bradycardia, has been described at extreme diving depth as well as at shallow depth either at sea or in the hyperbaric chamber (8, 30), or even during face immersion after submaximal exercise (2, 8, 9, 10). In contrast, an increase in CO has been reported during diving at 20 meters of depth or breath holding at thermoneutral conditions (8, 21, 29). In our study we did not observe bradycardia. Analyzing the HR trend along the four epochs, we observed no significant changes among all the epochs, with the exception of only a slight increase of HR from epoch I (resting condition before preparation and subsequent BH) to epoch II (average 1.2 min during BH), possibly related to the preparation maneuvers and/or psychological tension. In our opinion, the main reason for the lack of bradycardia was the performance of BH in air rather than in water. Andersson et al. (1) have shown that in air, BH attenuates, but does not abolish, the bradycardia elicited by apnea with face immersion (1). Differently from the study of Andersson et al., in which the experimental conditions were similar to ours but HR was monitored beat by beat, we did not analyze HR beat by beat but averaged HR at predefined epochs, when hemodynamic and CMR parameters were assessed simultaneously. In particular, epoch II had an average time of 1.2 min that was already longer than the maximal BH time (40 s) in the study of Andersson et al. (1). Furthermore, HR response to breath hold may depend on different factors such as external stimuli, age, and diving
experience (19, 20, 22, 31, 32). As a matter of fact, in our study the most bradycardic response from *epoch II* to *epoch IV* was observed in the world champion Carlos Coste, whose HR progressively reduced from 78 beats/min (*epoch II*) to 72 beats/min (*epoch III*) and 64 beats/min (*epoch IV*) with a maximal BH time of 4.7 min.

Finally, although in the present study MBP increased significantly, previous studies have shown that hypertension is not a prerequisite for the apnea-induced bradycardia (11, 32) and that bradycardia may occur even in the absence of hypoxemia (19, 20).

**Conclusions.** The present study showed that in healthy diving athletes during breath holding in air, the stroke volume and cardiac output increased due to the recruitment of LV preload reserve, which counterbalanced the reduction in systolic function. The analysis of the time course of events makes us prone to consider these effects as the integrated cardiovascular response to different inputs including activation of the sympathovagal system, elicitation of mechanoreceptor, baroreceptor, and chemoreceptor mediated-reflexes, and acute hypoxemia, acting simultaneously or in rapid succession (6, 11).

**ACKNOWLEDGMENTS**

We thank the diving athletes, certified by Apnea Academy as divers, who participated to the study; Emiliano Bottoni, Alex Chiappe, Lorenzo Cirri, Marco Dalitulia, Massimiliano Farnesi, Giuseppe La Rosa, Manrico Nencetti, Marco Pertusati, Gianni Stecchi, and Carlos Coste (world record holders of constant weight), and also Paolo Orsini and Francesco Montanari for technical assistance. We also thank Danilo Cialoni of the Apnea Academy for his valid contribution in keeping contact with the athletes and arranging their schedules.

**REFERENCES**


