RENAL AND CIRCULATORY FACTORS IN THE EDEMA FORMATION OF CONGESTIVE HEART FAILURE[1]

By A. P. BRIGGS, D. M. FOWELL, W. F. HAMILTON, J. W. REMINGTON, N. C. WHEELER, AND J. A. WINSLOW

(From the Departments of Biochemistry, Physiology, and Medicine, University of Georgia School of Medicine, Augusta)

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While many contributions have been made to the study of heart failure, the basic factor initiating the chain of events leading to edema formation in that condition remains unidentified. It is hoped that this report will present evidence which may prove useful in elucidating the problem.

METHODS

All renal and circulatory studies to be reported were done on cardiac patients. Twenty-one patients were in heart failure at the time of the observations, while 18 were compensated cardiacs. In ten cases, studies were made in the same individual during failure and again after compensation had been restored. Patients were treated with digitalis, diuretics, bed-rest, and a low salt diet which, in actual ward experience, has not produced a very rigid restriction of sodium. Some patients had been on maintenance doses of digitalis prior to admission to the hospital. In these cases, digitalis was continued while other medication was withheld until initial studies were completed. When compensation was restored, as indicated by reduction of dyspnea and edema and maintenance of steady weight, all diuretic medication was withheld for at least 48 hours (in most cases for a much longer time), and the determinations were repeated.

The cardiac output was determined by the Fick principle, utilizing the technique of right heart catheterization (1). This involved estimation of arterial and mixed venous blood oxygen content, and oxygen consumption. From the oxygen content of arterial (A) and venous (V) blood, the approximate oxygen saturation of the mixed venous blood was calculated from the relation $V/A \times 100$. This tacitly assumes complete arterial saturation—which is near enough the truth for our purposes. Intracardiac pressures were measured by an optical manometer (2). Blood volume was measured with the dye T-1824 (3). The method used differed from that most frequently described in that the relation between dye dilution and optical density (at 625 mμ as measured in the Beckman spectrophotometer) was determined directly in the blood of the subject of each experiment. Standards were made up by diluting known amounts of the injected dye solution in whole blood, and the blood volume was calculated from these measurements, as compared with the optical density of a sample drawn ten minutes after dye injection. This procedure avoids the controversial errors inherent in the centrifuge hematocrit. Plasma volumes were not measured, because these are less constant than blood volume since they vary inversely with cell volume. Plasma volumes are a less direct measure of the fluid which distends the vascular tree and brings about some of the signs of congestive failure, than are blood volumes. The thiocyanate space was estimated by the method described by Crandall and Anderson (4) and modified by Gregersen and Stewart (5). Glomerular filtration rate was measured by the sodium thiosulfate clearance (6). Sodium was determined by the method of Bradbury (7). Since the sodium levels in the plasma were quite constant, the sodium excretion in milligrams can readily be estimated by multiplying the clearance figure by 3.22. Sodium clearances thus measured were the response of the kidneys to a rather large sodium load. This sodium load was the infusion of a little less than 500 cc. of 1.6% sodium thiosulfate. A 15-minute period for equilibration was allowed before starting the clearance test. At this time the level of serum sodium was found to have returned to the control value. Because of various technical difficulties, all the above observations were not always obtained in a given case. When body size corrections were made, the trends described below were not changed. Weight changes during an experiment were large, and it was decided to record the figures on an individual rather than on a body size basis.

RESULTS

Figure 1 shows the relation of the filtration rate to the sodium resorbed, and to the sodium clearance, in uncompensated and compensated individuals. The points indicating sodium resorbed correlate very closely with filtration rate (8), but neither filtration rate nor the amount of sodium resorbed shows any consistent change which is related to whether the patient is compensated or uncompensated. The ability to excrete sodium, on the other hand, consistently improves as the patient regains compensation.

Thiocyanate space is definitely greater in uncompensated than compensated patients (Table I). The kidneys of the compensated patients are able

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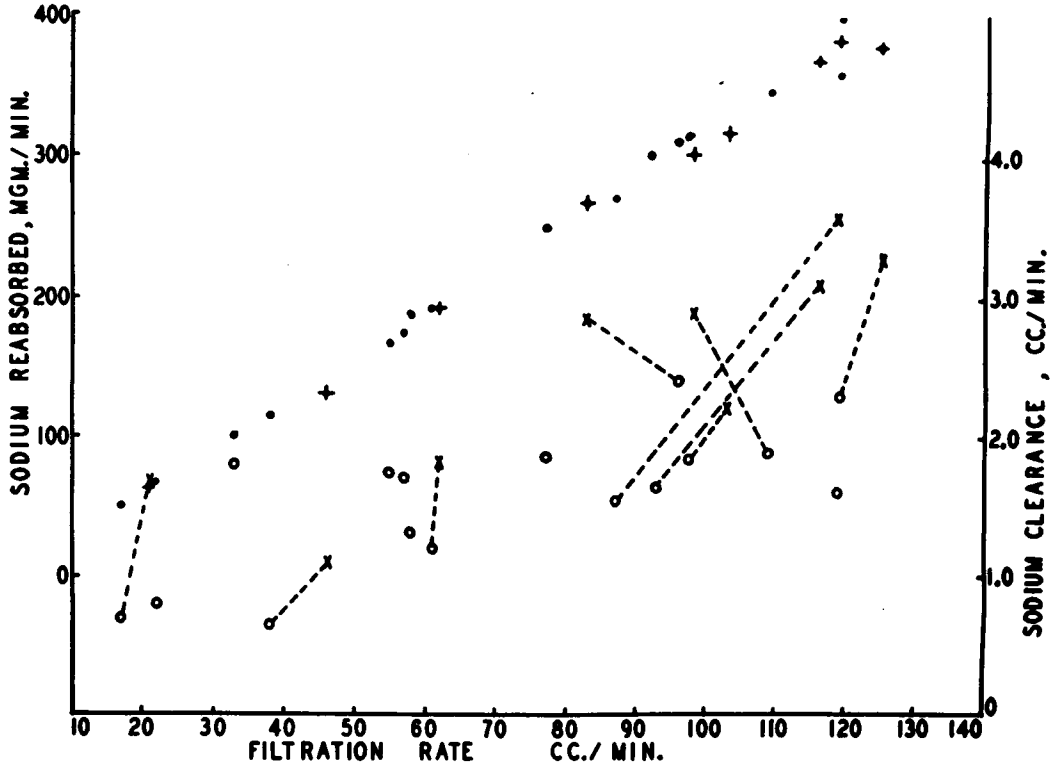

FIG. 1. THE RELATIONS BETWEEN SODIUM REABSORBED AND FILTRATION RATE IN UNCOMPENSATED (•) AND RECOMPENSATED (+) PATIENTS, AND THE RELATION BETWEEN SODIUM CLEARANCE AND FILTRATION RATE IN UNCOMPENSATED (o) AND RECOMPENSATED PATIENTS (x)

Dotted lines connect determinations on the same patient.

to excrete sodium at nearly twice the rate of those of the uncompensated patients. Regaining the ability to excrete sodium goes hand in hand with the reduction in thiocyanate space (Figure 2). The standard errors (Table I) are large because of the natural variability of the data. The increase seen in each case with recompensation (Figure 2) indicates that there is a significant change in the ability to excrete sodium. No relationship could be found between filtration rate and thiocyanate space.

Blood volume changes, unlike those of thiocyanate space, were inconsistent, and the averages for the two groups are not different (Table I). The presence of inanition, on entrance, in many cases, no doubt played a complicating role in the blood volume changes. The average arterial oxygen content, for example, is definitely lower in un-

TABLE I

Renal and circulatory data from a series of uncompensated and recompensated cardiac patients

Type of patients		Sodium thiocyanate space	Blood volume	Serum sodium	Filtration rate	Sodium clearance	Right ventricle filling pressure	Oxygen consumption	Arterial blood oxygen	A-V oxygen difference	Cardiac output	Venous oxygen saturation
		L.	*L.*	*mgm./100 cc.*	*cc./min.*	*cc./min.*	*mm. Hg*	*cc./min.*	*vols./100 cc.*	*vols./100 cc.*	*L./min.*	*per cent*
Uncompensated	No.	14	12	14	14	14	13	17	16	14	14	14
	Mean	27.8	5.30	324	70.0	1.35	15	261	15.60	7.3	3.8	55
	S. E.	*1.9*	*.33*	*2*	*9.2*	*.13*	*3*	*15*	*1.00*	*0.5*	*0.4*	*2*
Recompensated	No.	9	10	10	10	9	6	11	11	11	11	11
	Mean	20.2	5.27	319	81.2	2.31	9	252	17.52	5.7	4.7	67
	S. E.	*1.5*	*.30*	*4*	*11.0*	*.29*	*2*	*6*	*0.80*	*0.3*	*0.4*	*1*

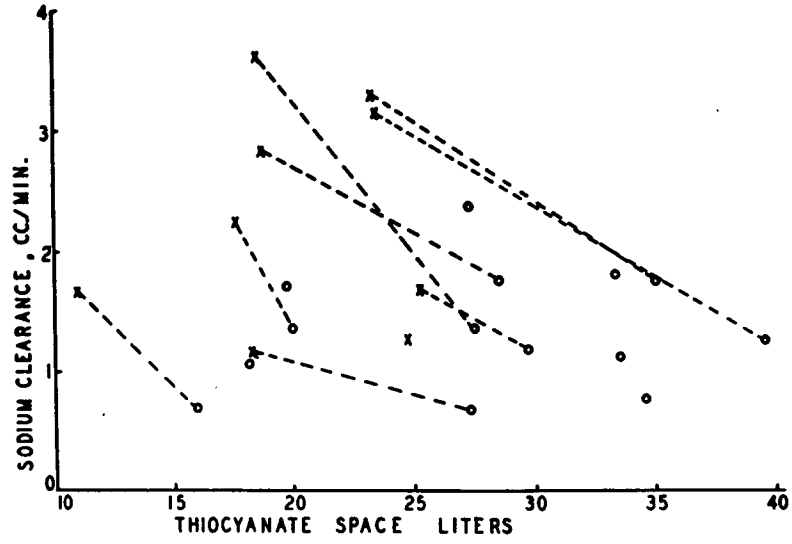

FIG. 2. THE RELATION BETWEEN THIOCYANATE SPACE AND SODIUM CLEARANCE IN UNCOMPENSATED (o) AND RECOMPENSATED (x) CASES
Dotted lines connect determinations in the same subject.

compensated than in compensated cases. Favorable changes in nutrition and water balance, and, in extreme anemias, transfusions, can account for the hemoglobin increase on compensation.

The filling pressures of the right ventricle were higher in uncompensated than in recompensated cases (Table I). The pressure did not always decrease as compensation was regained, nor was there any definite correlation between pressure height and the thiocyanate space, as might be expected if the one were the primary factor leading to an increase in the other. There was little statistical significance in the difference between the means of the pressures in compensated and recompensated cases.

The cardiac output values for the uncompensated group are placed in two categories. Two of 16 cases showed failure in the presence of an abnormally high output, and with unusually high mixed venous blood oxygen content. One of these patients probably had beri-beri, while the other failed from unknown causes. Only one of these patients could be studied after compensation was restored, and he showed a fall in cardiac output, thiocyanate space, blood volume and right heart filling pressure, with an increase in sodium clearance. Our knowledge of congestive heart failure is too inadequate to allow successful integration of these two unusual cases into the picture as a whole. It should also be pointed out that in both these cases, the venous sample was obtained from the right atrium, so that incomplete mixing may have contributed to the high venous oxygen content.

Even with these two cases included, the average output is higher in the compensated than in uncompensated cases. There is, however, considerable overlap (Figure 3), and compensation is not necessarily accompanied by an increase in output. Excluding the high output failures (Table I),

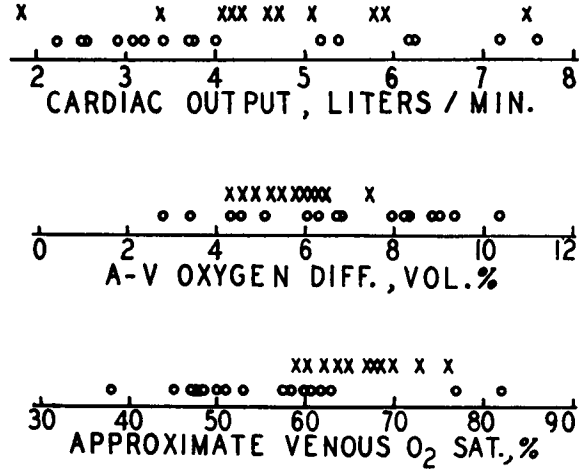

FIG. 3. DISTRIBUTION OF CARDIAC OUTPUT, A-V OXYGEN DIFFERENCE, AND APPROXIMATE OXYGEN SATURATION OF MIXED VENOUS BLOOD, IN UNCOMPENSATED (o) AND RECOMPENSATED (x) CASES

the means of the uncompensated and recompensated cases differed by an amount that is significant at the 10% level.

The arterio-venous oxygen difference is definitely larger in the uncompensated cases than it is in the compensated cases. The difference of the two means is significant at better than the 3% level, but there is considerable overlap between the two groups and the change on compensation of a given individual was not always consistent.

The approximate venous oxygen saturation increased consistently as compensation was regained. Statistically the difference between the means of the uncompensated and recompensated groups was highly significant ($P < 0.001$).

DISCUSSION

During recent years attention has been focused on the kidneys as playing an important role in the edema formation of congestive heart failure (8–15). The underlying mechanism by which the failing circulation causes the kidney to excrete sodium and water in inadequate amounts has been the subject of considerable speculation. However, it would seem to be well as a preliminary step to inquire into the manner in which renal function is disturbed, before discussing the mechanism of this disturbance.

It is, of course, difficult to decide whether the renal dysfunction seen in congestive failure is due to renal impairment or to circulatory disturbance. None of the patients were uremic and most of them were capable of secreting urine whose specific gravity was above 1.02; but the low thiosulfate clearance in the compensated state is, itself, good evidence of renal impairment.

Warren and Stead (12) pointed to the diminished renal blood flow which they noted in congestive heart failure. Merrill (9), following out this concept of "forward failure," found a decreased filtration rate in patients with congestive heart failure as compared to normal, and so concluded that the diminished excretion of sodium came about simply because a smaller amount was filtered. Mokotoff *et al.* (8) have supported this view with the further observation that sodium resorbed varied directly with filtration rate, and that the latter was less in cardiacs than in normal individuals.

One should not attribute much significance to the fact that filtration rate and resorbed sodium are proportional. It should be remembered that relatively huge quantities of salt and water are filtered and reabsorbed, even by a handicapped kidney, in comparison to the small amounts excreted. This rather close correlation between filtration rate and sodium resorption is explained by the manner in which the figures are derived. The amount of sodium resorbed is calculated by subtracting the quantity of sodium eliminated in the urine from the amount filtered. The urinary sodium is a relatively small quantity, which causes a negligible diminution in the figure for the amount filtered. The sodium filtered is obtained by multiplying the plasma sodium level by the filtration rate. The plasma sodium is held within narrow limits. Thus plotting sodium resorbed against filtration rate is not unlike plotting filtration rate against filtration rate times a constant, inevitably giving the picture seen in Figure 1 (• +).

Our data confirm the findings of Warren and Stead (12), of Merrill (9) and of Mokotoff and his collaborators (8) that the filtration rate in cardiacs is much less than it is in normal individuals. It must be emphasized, however, that patients can regain clinical compensation without in any significant degree increasing their filtration rate.

These findings in relation to filtration rate coincide with those of Seymour *et al.* (15) who studied six patients in congestive failure. They found that as the patients regained compensation the filtration rate was decreased in one and increased in four, but in only one of these was the increase significant in amount. Thus the filtration rate has an ambiguous relation to the state of compensation in cardiac patients. There is a widely varying amount of sodium filtered and consequently a widely varying amount of sodium presented to the tubules of the several patients. The amount of sodium presented varies over a range which is nearly equal whether the patient is uncompensated or recompensated, and since it is nearly all resorbed, there is a similar wide variation in the amount of sodium reabsorbed.

The ability to excrete sodium, on the other hand, always increased after compensation had been regained. The experiments showing this (Figures 1 and 2) are the more conclusive in that the sodium clearance is higher after compensation in spite of

the fact that the patients had been on salt restriction and had received the same test load of sodium as they received when they were admitted in the uncompensated state. The total sodium load was greater therefore when they were uncompensated and the sodium clearance was smaller.

From the mean figures of Table I, it may be calculated that the over-all rise in filtration of sodium was about 36 mgm. per minute, which is sufficient to account for the increase in sodium excretion of about 3.1 mgm. per minute. But, it is not necessary to assume, as some workers have, that the extra excretion is due to extra filtration. For, in the first place, if the extra sodium filtered were resorbed to the usual extent of about 99%, then only about 0.3 mgm. extra sodium per minute would have been excreted. Secondly, extra sodium is excreted in some cases without an increase in filtration. And thirdly, a seemingly minor variation in per cent sodium resorption may represent a great variation in sodium excretion, involving several grams per day, and, therefore, possibly large volumes of excreted water. Some factor connected with the state of uncompensation may force the kidney to resorb sodium and water not necessarily in greater amount but more *completely.*

It is reasonable to suppose that this factor is related to the circulatory states of the patients. Of the various circulatory findings which we have compared there is an improvement in oxygen capacity as measured by arterial oxygen content, in cardiac output and in A-V difference. As seen above, changes in these categories are not so consistent as are changes in oxygen saturation of the mixed venous blood. Here there is a good distinction between compensated and uncompensated cases. A lowered venous oxygen saturation appears to be a definite part of the usual picture of congestive heart failure, and is a deficiency which was corrected in the process of recovery in all of our patients. This implies that during failure the cells of the body are subjected to an environment having an abnormally low oxygen concentration—a true hypoxia. In extracting oxygen from this medium to carry on vital processes, the tissues of the uncompensated cardiac are at a disadvantage, suggesting a handicap to normal cellular activity.

The oxygen saturation of the mixed venous blood represents the conditions under which the tissues are working. To illustrate, let us use the average figures for per cent oxygen saturation of the venous blood. This average for the uncompensated group is 53%, which, when applied to the oxygen dissociation curve, represents an oxygen tension of 28 mm. The figure of about 67% in compensation gives a venous oxygen tension of about 35 mm. This ignores differences in carbon dioxide tension between the two groups, which would narrow the differences slightly. From this, applying Henry's law, it appears that the fluid medium surrounding the tissue cells contains a lower concentration of oxygen in heart failure than otherwise.

The organism, threatened with hypoxia, may react in several different ways. The oxygen consumption may fall as is the case in the children afflicted with congenital heart disease of the cyanotic group (16). The cardiac output may rise as is the case in severe anemia and hyperthyroidism. The hemoglobin may increase as is the case at high altitudes or in congenital heart disease. Another mechanism may be available, which usually ends in a vicious cycle. The kidney may conserve water and salt. Increased tubular reabsorption is seen as a result of afferent nerve stimulation and exercise (17). In response to a short-lasting episode this may help in conserving the blood volume and in increasing the circulation rate; as a chronic response it may lead to edema and congestive failure of the circulation.

Our patients in the uncompensated condition showed a lowered cardiac output, a reduced hemoglobin and an increased oxygen consumption. The increase in the oxygen consumption is probably due to dyspnea, restlessness, and other discomforts attendant upon the disease. These would tend to increase the cardiac output. The weakened heart can only partially meet this demand for more blood, so that the A-V differences rise, and the oxygen saturation of the mixed venous blood falls.

Lowered hemoglobin has a similar effect upon the cardiac output and venous oxygen saturation, but not upon the A-V difference. For example, one patient had an arterial oxygen of 8.20 vol. %. His venous oxygen was 3.15 vol. %, giving a relatively low A-V difference and relatively high cardiac output. His approximate venous oxygen saturation was 38%, a very low figure. On compensation, and with a higher hemoglobin, the cardiac output and A-V difference did not change for

the better but the venous oxygen saturation was raised to a figure representative of the compensated group. Anemia may give rise to oxygen saturation of the mixed venous blood that is well below the figure of 60%. Thus Brannon *et al.* (18) report data in which four of their cases have saturations between 40 and 50% with no mention of uncompensation. It is recognized that anemia predisposes to dyspnea and edema even when the cardiac output is high. Studies of renal physiology in such cases will be of great interest.

It should be mentioned that Fahr and Ershler (19) deny the importance of anoxia in the production of edema on the ground that congenital heart cases of the cyanotic group may not have edema even with a low arterial oxygen saturation. The tremendous increase in hemoglobin seen in these cases prevents the venous blood from becoming extremely unsaturated. The figures in so far as they are obtainable indicate that the saturation of the mixed venous blood is within normal limits or on the border line. Thus in two cases of Tetralogy of Fallot reported by Dexter *et al.* (20) the oxygen saturation of right atrial blood was 73% and 59%, while that in one such case observed by us was 60%. Figure 3 shows that the dividing line between cardiacs with and without edema falls at about 60% saturation of the mixed venous blood. Therefore there is no reason to expect such patients to show edema on the basis of their hypoxia.

The well-recognized benefit from the administration of oxygen in congestive failure with obstruction anoxia from pulmonary edema is also pertinent. Barack and Richards (21) have shown that oxygen administration will diminish edema which may return on cessation of the treatment.

It is conceivable that anoxia might increase the permeability of the capillaries so that there is a local production of edema by the filtration of a plasma-like fluid into the tissue space. The fact, however, that the protein content of the edema fluid in cardiac cases is very low leads to the conclusion that a normal capillary barrier is maintained in congestive failure.

It seems more likely that the edema is formed from ingested water which cannot get out through the kidneys. It is well known that water, administered by vein or by mouth, will be stored in the extravascular spaces until the kidney removes it. Its removal is brought about by lessening the reabsorptive capacity of the kidney. The inability of the kidney in congestive failure to get rid of edema fluid, we believe, is due to an overworking of the mechanism which reabsorbs salt and water, and this in turn seems to be closely related to cellular hypoxia.

The manner in which cellular hypoxia causes more complete tubular reabsorption and leads to the edema is difficult to understand. The idea that changes in renal activity are brought about by the direct effect of anoxia upon the kidney is probably ruled out by the fact that the oxygen tension of renal vein blood in congestive failure may be within normal limits (9). With reduction in blood flow the oxygen consumption must be reduced or the A-V difference increased. In any case an abnormality of renal function is evident.

It seems likely that hormonal influences may play a role in effecting a more complete tubular reabsorption. Fremont-Smith (10) postulated an increased "antidiuretic factor" which prevents, in edematous patients, the diuresis which normally follows the ingestion of water. Taking water, in these cases, causes a greater than normal blood dilution. The source of such an antidiuretic principle may be the posterior pituitary gland (22), which is known to secrete an antidiuretic hormone in times of stress (17).

Numerous observers have assessed the effect of adreno-cortical steroids and similar substances in increasing the action of the kidney to reabsorb sodium and water. Edema may be produced as a result of overdosage of desoxycorticosterone, or sex hormones (23, 24).

The classical idea that an excess of hydrostatic over osmotic pressure in the systemic capillaries is a primary factor in the production of cardiac edema does not receive support from these observations. Right auricular pressure, though higher than normal, was not consistently higher in the uncompensated cases than it was in the compensated cases. Moreover Altschule (25) presents a series of cases of cardiac edema in which the venous pressure is within normal limits. He also reviews many such cases from the literature.

It is quite probable that once failure is established, increased venous pressure (resulting in increased capillary hydrostatic pressure) and lowered plasma proteins, which are seen in many cases

of congestive failure, contribute to the persistence and perhaps to the increase of the edema.

The evidence presented above, however, indicates that the circulatory disturbance produces a reduced oxygen tension in the mixed venous blood, and that this brings about in some way a more complete resorption of salt and water by the kidney, which in turn is responsible for the edema.

SUMMARY

1. Studies are reported on 21 patients during congestive heart failure, and on 18 patients with heart disease but no signs of failure. In ten individuals duplicate studies were obtained both before and after compensation was restored.

2. These data do not support the theory that edema fluid is eliminated in these patients by increased filtration in the kidney. Rather they point to a less complete tubular resorption of sodium and water as the important factor.

3. On the basis of our circulatory data, the uncompensated patients were most clearly distinguished from the recompensated patients by their lowered mixed venous oxygen tension, suggesting that this handicap to cellular respiration is related to the symptomatology of congestive heart failure.

4. That the reduced sodium clearance, increased thiocyanate space, and lowered venous oxygen tension, in failure, are causally related is suggested, and possible mechanisms of their inter-relation are discussed.

5. Secondary factors which may contribute to the edema in a given case of congestive heart failure have been briefly mentioned.

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