Role of the Endocardial Endothelium in the
Regulation of Myocardial Function
Physiologic and Pathophysiologic Implications

Stefan G. De Hert, M.D., Ph.D.,* Thierry C. Gillebert, M.D., Ph.D.,† Luc J. Andries,‡ Dirk L. Brutsaert, M.D., Ph.D.§

IMPAIRED mechanical performance of the heart is one of the leading causes of mortality in the western world. It constitutes a major risk factor in many patients presenting for anesthesia and surgery. Thorough knowledge of the mechanisms underlying contractile behavior of the heart is, therefore, an important issue for physicians dealing with patients with impaired cardiac performance.

Myocardial function is modulated by extracardiac (innervation, circulating catecholamines, renin-angio-
tensin system, atrial natriuretic factor, prostaglandins) and cardiac regulatory mechanisms (Frank-Starling mechanism and contractility). In the course of cardiac dysfunction, several compensatory mechanisms are elicited. These include extracardiac compensatory mechanisms, which are primarily based on activation of various hormonal systems and cardiac compensatory mechanisms, such as myocardial hypertrophy, dilatation of the ventricle, and adaptation of myocardial biochemistry.

Recently, growing in vitro and in vivo experimental evidence has indicated that the endocardium is also involved in the regulation of myocardial function. This role of the endocardium, and particularly the endocardial endothelium (EE), involves both the extrinsic cardiac regulatory mechanisms as a mediator of the myocardial action of several hormones and circulating elements in the blood, and the intrinsic regulatory mechanisms as one of the direct modulators of myocardial function. This article will review the experimental evidence of the role of EE as a regulator of myocardial function.

Endocardial Endothelium

Morphology
The cavitary side of the heart is covered by the endocardium. Endocardial thickness varies with localization. Normal endocardium is thicker in the atria than in the ventricles, and endocardial collagen and elastic fibers are more abundant in the outflow tracts of the ventricles than in the inflow tract. These regional differences have been related to differences in pressure or shear stress.1,2

The endocardium can be divided into two layers, the endocardium proper and the subendocardium. The subendocardium lies between the endocardium and the

* Head of the Division of Cardiac Anesthesia, Department of Anesthesiology.
† Associate Professor, Department of Physiology and Medicine.
‡ Research Fellow, Department of Physiology and Medicine.
§ Professor and Head, Department of Physiology and Medicine.

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Address reprint requests to Dr. De Hert: Department of Anesthesiology, Division of Cardiac Anesthesia, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium.

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myocardium. It contains, primarily, thick collagen fibers and small blood vessels, but also some elastic fibers. The endocardium proper can be further subdivided into the endothelial layer, the basement membrane, and a subendothelial fibroelastic layer with collagen and elastic fibers, fibroblasts, few smooth muscle cells, and pinocytotic vesicles. In vertebrates, EE constitutes a uniform, continuous layer of flat and polygonal cells. These cells have bulging nuclei and are closely approximated (fig. 1). The EE cells lie on a thin basal membrane. They contain a variable number of microvilli, small protrusions, and discrete membrane invaginations. The number and distribution of these surface structures vary with the site in the heart. The number of stress fibers and the orientation and cell shape of EE cells also appear to be highly variable. For vascular endothelium, the alignment of endothelial cells and the number of stress fibers have been correlated with shear stress of the blood flow. This mechanism has also been invoked for the number of stress fibers in EE cells, but other factors, such as regional differences in composition and alignment of underlying connective tissue or mechanical deformation of the ventricular wall surface during contraction, may also affect cell shape and stress fiber organization in the EE cells. Other elements of the cytoskeleton, such as vimentin filaments and microtubules, are organized differently in EE compared with vascular endothelium. The presence of structured contractile proteins within EE cells indicates the possibility for shape changes and some degree of motility.

There is extensive intercellular overlap between junctional areas of EE cells. This feature is more pronounced than for coronary vascular endothelium. Gap junctions are present between EE cells. They are especially prominent in the junctional areas. EE cells contain numerous organelles. The Golgi-apparatus is well developed, but the number of smooth vesicles appears to be lower than in capillary endothelium.

**Functional Role of Endocardial Endothelium**

The trabecular structure of the cavity side of the heart, and the surface characteristics of EE cells with their numerous microvilli and invaginations, offer a high ratio of cavitory surface area to ventricular volume. This strategic anatomic position is indicative of a possible role of EE in the regulation of performance of the adjacent myocardium. From the embryologic, as well as the phylogenetic, point of view, it appears that EE is, at least at certain times during development of the cardiovascular system, more than a simple anatomic barrier between blood and myocardium. In the embryo, the endocardial endothelial monolayer constitutes the earliest structure of the future heart. Its development precedes that of myocardium, coronary vessels, conducting fibers, and autonomic innervation. During further development, the endocardial plexus becomes surrounded by a one- to two-cells-thick mesodermic
layer. The wall of the cardiac tube then consists of a single layer of endothelial cells, separated from the external myocardial mantle by a relatively thick, acellular, and almost structureless third layer, called cardiac jelly. In the primitive heart, the endocardial monolayer and the underlying cardiac jelly separate the myocardium from the lumen, and substances from the blood are exchanged with the myocardium through endocardium and cardiac jelly. Later, the primitive myocardium develops extensive intercellular or intertrabecular sinusoids through which substances can diffuse. Transport of substances by the sinusoidal circulation is subsequently replaced by the coronary circulation.9,10

A possible functional role for EE is also apparent from the phylogenic development. In lower species, such as the frog, there is no coronary circulation in the myocardium, and exchange of substances between luminal blood and myocardium is exclusively accomplished through the endothelial cellular layer of the endocardium.11 In fish and reptiles, capillaries are present only in the epicardial and outer compact regions of the ventricular wall.12 Only in higher species does the coronary circulation become well developed, supplying oxygen and other substrates to the myocardium.12

Despite the hypothesis that EE appears to have played an important role during embryologic and phylogenetic development, its functional importance in adult mammalian physiology has long been underestimated. Endocardial endothelium has long been considered a barrier between the superfusing blood and the myocardium without active function. Over the years, EE has been attributed a passive mechanical function in preventing compression of subendocardial vasculature.13 It has also been suggested that the endocardial endothelium may have electrophysiologic, anticoagulant, and fibrinolytic properties, and may play a role in water and ion exchange and in ATP and glycogen metabolism.8,13 Only in 1986 was it first demonstrated that EE also constitutes a structure that actively regulates myocardial performance.14 This evidence was first gathered in in vitro studies on isolated papillary muscles of the heart, and was later confirmed in vivo in an open-chest canine model.

In Vitro Studies. Various chemical, mechanical, and pharmacologic methods were developed to damage EE in vitro. Of these, irradiation with high-power (5 W/cm²), high-frequency (0.9 MHz), continuous-wave ultrasound has been shown to damage EE most selectively.15 Regardless of the method used, selective damage of EE of isolated papillary muscle resulted in an immediate and irreversible abbreviation of isometric twitch duration, and was accompanied by a decline in peak isometric twitch tension. In other words, the presence of an intact EE modulated performance of myocardium with a prolongation of isometric twitch duration, with concomitant increase in peak twitch performance, without significantly affecting Vmax14-16 (fig. 2). Vmax is the maximal velocity of unloaded muscle shortening, and is widely used as a measurement of contraction velocity.

Inotropic effects of different substances (α1 and β agonists, angiotensin II, adenosine, ATP, vasopressin, 5-hydroxytryptamine, and endothelin) have been shown to be mediated directly through receptors on myocardial cells.17,18 Because EE is continuously exposed to the superfusing blood, it has been hypothesized that EE could also sense and transmit some of the inotropic effects of hormones. This hypothesis has been confirmed by experimental evidence.

Atrial natriuretic factor (ANF) has been shown to directly affect isolated cardiac muscle.19 Atrial natriuretic factor diminished peak twitch contraction and induced early tension decline with no changes in Vmax. This response was similar to suppression of myocardial function after removal of EE. The inotropic effect of ANF was mediated through EE as it disappeared after damaging EE. This indicated that ANF may act on the myocardium through receptors localized on the EE.19 It is worthwhile to mention that dense receptors for ANF have been found on the ventricular endothelium.20 These receptors could mediate the observed response, possibly through release by EE of a relaxing factor. In vascular smooth muscle, the action of ANF is accompanied by an increase in intracellular guanosine 3',5'-cyclic monophosphate (cGMP). The similarities between the effects on myocardial performance induced by the removal of functional endothelium and those induced by dibutyryl cGMP (a cGMP analog known to cross cell membranes), by sodium nitroprusside (a drug that increases intracellular cGMP), or by ANF indicate that alterations in intracellular cGMP may somehow be implicated in the endocardium-mediated control of cardiac performance.6,19

There is also experimental evidence that some of the effects of catecholamines on myocardial muscle are EE mediated.21 Under β blockade, low concentrations of the α1-agonist phenylephrine have been shown to induce a marked positive inotropic response with typical prolongation of the twitches, but with no change in Vmax. This response was opposite to the effects of ANF,
and similar to what would be expected from positive activation of the endocardium-mediated control of cardiac performance. The α₁-agonist positive inotropic effect was abolished after treatment with prazosin, but also after damaging the endocardial surface; therefore, this cardiac α₁-agonist activity seemed to be mediated through EE.²¹

Vasopressin (ADH) induced premature tension decline during relaxation with decrease in twitch duration and peak twitch tension in muscles with intact EE.²² By contrast, after damage to the endocardium, addition of vasopressin induced a significant positive inotropic effect, with increase in total isometric twitch tension and Vmax, but without prolongation of the twitch duration. Hence, the observed inotropic effects of vasopressin depended on the presence of intact EE.²² Serotonin or 5-hydroxytryptamine and adenosine triphosphate (ATP) also caused a more pronounced positive inotropic effect in muscles with damaged endocardium, compared with the preparations with intact EE.²³ An intact EE, therefore, prevented the expression of the positive inotropic effects of adding vasopressin, serotonin, and ATP to the bathing solution.

A more complex interaction with EE has been revealed with angiotensin I and II.²⁴ After the addition of angiotensin I and II, a significant positive inotropic effect has been observed both in the presence and in the absence of an intact EE. In muscles with intact EE, addition of the angiotensin-converting enzyme inhibitor, captopril, significantly decreased the response to angiotensin II. By contrast, in muscles with a damaged EE, a captopril-induced potentiation of the response was observed. This means that an intact EE also prevented the captopril-induced inotropic potentiation of angiotensin II. This phenomenon of captopril-induced sensitization and desensitization was prevented by the administration of indomethacin.²⁴ This could indicate that stimulation of prostaglandin synthesis is the mediator of these phenomenon. However, this is only a hypothesis, and further investigation is needed to determine the exact mechanism of such a captopril-revealed prostaglandin–angiotensin interaction and to what extent a captopril-induced decreased breakdown of bradykinin or of other tachykinins would either directly or indirectly participate in these responses.

Aggregation of platelets has been shown to increase contractile performance.²⁵ This performance was significantly increased when EE was destroyed. How the intact EE partly suppresses and slightly modifies the direct effect of the aggregating platelets on the subjacent myocardium is unknown. The modulatory role of EE in this study was not explained by the synthesis of arachidonic acid metabolites, such as prostacyclin, because cyclooxygenase inhibition with indomethacin failed to alter the inhibitory effects of an intact endocardium.²⁵ Platelet aggregation resulted in the release
of several substances, including serotonin, adenosine diphosphate (ADP), ATP, calcium, and thromboxane A2. Inotropic responses to serotonin and to ATP (but not to ADP) were found to be significantly greater in the absence of an intact endocardium. The possible mechanisms involved in the modulatory role of EE in the platelet–myocardial cell interaction, however, remain speculative.

In conclusion, these different studies in isolated papillary muscle revealed that: (1) EE modulates performance of subjacent myocardium, and (2) EE senses and mediates, at least in part, some of the inotropic effects of different circulating elements in the blood.

**In Vivo Studies.** Based on the previously discussed data, it was hypothesized that the presence of a normally functioning EE may play a substantial role in *in vivo* cardiac physiology and pathophysiology. It could be expected that an intact EE would increase systolic performance by increasing ejection duration. This hypothesis has recently been confirmed in an open-chest canine model. Selective inactivation of normal EE function by intracavitary irradiation with high-power, high-frequency, continuous-wave ultrasound affected *in vivo* ventricular performance with shortening of ventricular ejection duration and decrease of systolic ventricular function.26 In other words, presence of a functional intact EE prolonged ejection duration and delayed relaxation. These *in vivo* effects appeared to be transient and reproducible, so that the method could be used to quantitatively assess EE modulation of cardiac performance in various physiopharmacologic circumstances.

Regulation of ventricular function by EE acts in continuous interplay with other regulators of ventricular function, such as regulation by volume and regulation by contractility. Functional effects of the intact EE were more pronounced when left ventricular end-diastolic pressure (LVEDP) was lower27 (fig. 3). This interaction between regulation of myocardial performance by volume and by EE indicated that ventricular function could be particularly dependent on EE integrity when circulating volume was decreased. The reasons why the magnitude of modulation of myocardial function by EE depended on prevailing ventricular volume are, as yet, speculative. A common underlying mechanism has been suggested.16 It could be that, similar to that for length modulation of myocardial function,28,29 endocardial modulation of cardiac performance may be mediated through changes in the sensitivity of the contractile proteins for calcium. This hypothesis has been endorsed by recent experiments demonstrating that EE modulated calcium responsiveness of myocardial myofilaments.30 If length modulation and endocardial modulation would act via the same mechanism, it is conceivable that, when length modulation of myocardial performance is maximized, the effects of endocardial modulation would become less pronounced.

Functional effects of intact EE were also more pronounced at lower calcium27 (fig. 4). The physiologic mechanism of the protective action of high calcium against EE-mediated changes in myocardial function remains to be established. Calcium has been shown to play a role in preserving functional and structural integrity of cellular membranes and intercellular connections; sealing processes also appear to depend largely on calcium.31,32 Therefore, it has been hypothesized that the protective action of calcium may, perhaps, be based on its membrane-stabilizing properties. Whether this is the only effect of calcium, or some interaction between modulation by EE and calcium
Fig. 4. Effects of transient inactivation of normal endocardial endothelial function at two different inotropic states: (1) baseline, and (2) after intravenous administration of calcium. Inactivation of normal endocardial function (dashed lines) decreased ejection duration. This effect was significantly less pronounced after calcium.

metabolism downstream to the EE cells is involved, is still under investigation.

Regulation of myocardial function by EE also appeared to interact with some aspects of humoral control of myocardial function. Functional effects of intact EE appeared more pronounced under selective $\alpha_1$ agonism with low-dose phenylephrine after pretreatment with $\beta$ blockade to suppress $\beta$ agonist activity of phenylephrine. It was, therefore, suggested that at least part of the inotropic activity of phenylephrine may be mediated through EE. How the positive inotropic effects of phenylephrine could be part of a cascade of EE-dependent events, however still remains to be elucidated.

**Physiologic Mechanism of Endocardial Function.** At least three possible ways can be hypothesized for the mechanisms involved in EE modulation: EE may act as an electrochemical barrier, may release chemical substances or messengers, or may exert its influence by a combination of both (fig. 5).

**Physicochemical Control.** Endocardial endothelium cells exhibit important intercellular overlap. These intercellular connections are lined by a negatively charged glycocalyx layer, and this may offer specific permeability features. Differences in tracer permeability have been found between EE and subendocardial vascular endothelium. It has been suggested that these differences may result from differences in hydrostatic pressures. Electrical charge of the various tracers affected vascular and endocardial transendothelial penetration, indicating that charge may also influence

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trans-EE permeability. The differences in permeability between EE and coronary endothelium in the subendocardial myocardium may assign characteristic electrochemical properties to the endocardium. As an electrochemical barrier with variable permeability, the endocardium could control homeostasis of the microenvironment of the interstitial fluid surrounding the cardiac muscle cells. Ion channels and transmembrane potentials have been demonstrated in vascular endothelial cells. There is also experimental evidence for the existence of a transmembrane potential and of ion channels in EE cells. The presence of gap junctions between the EE cells indicates electrochemical coupling of these cells. For vascular endothelial cells, gap junctions have also been described between endothelial cells and smooth muscle cells. However, until now, no such phenomenon has been found for endothelial cells.

Although, until now, firm experimental evidence was lacking, all of these features indicate a possible role for the endocardium to act as an electrochemical barrier between the superfusing blood and the underlying myocardium.

**Release of Endocardial Substances.** It is tempting, in analogy to vascular endothelium, to suggest the existence of endocardially released inotropic factors. The presence of a functional EE delays the onset of isometric tension decline and shifts the [Ca]_tension curves and the length-tension curves upward and to the left. This effect is reversibly abolished after removal of a functional endocardium. It may, therefore, be speculated that EE releases a positive inotropic factor that would increase the sensitivity of contractile proteins to calcium (myocardium contracting factor [MCF]). Similarly, EE may produce and release another factor that decreases sensitivity of the contractile proteins for calcium and induces relaxation (myocardium relaxing factor [MRF]). The relative amount of these factors would then represent the EE contribution to muscular twitch duration and left ventricular ejection duration. This hypothesis was recently endorsed by experimental evidence that EE also releases substances with inotropic properties. Effluent from superfused cultured EE cells was bioassayed with EE-deprived papillary muscles. These cells tonically released an unstable endothelium-derived relaxing factor (EDRF)-like substance (MRF) and an as-yet-unidentified stable substance that reversed the changes in myocardial performance seen after EE removal (MCF). In addition, in isolated ferret papillary muscles, EE could be stimulated by substance P to release an EDRF-like agent that elevated myocardial cGMP, whereas removal of EE was mimicked by (but not associated with) elevation of myocardial cGMP. It was demonstrated that EE cells of cardiac valves continuously release an EDRF. Other recent experiments revealed that cultured endocardial cells possess the ability to synthesize nitric oxide (NO), indicating a role of NO in modulation by EE. Tonic EDRF activity, however, appeared to be low, because inhibition of EDRF synthesis by N^G^-monomethyl-L-arginine did not alter twitch duration in isolated cardiac muscle. Release of prostacyclin by EE may also contribute to MRF activity. Tissue cyclooxygenase was found to be twice as high in the endocardium as in the myocardium, and was localized specifically in the endothelial cells. In addition, EE from isolated cardiac valves, as well as valvular EE cells, in culture produce prostacyclin. Whether still other factors than NO and prostacyclin are involved in the MRF activity of EE is not known at present.

Myocardium contracting factor has been termed endocardin, and has a greater stability than NO and prostacyclin. However, its exact nature has not yet been identified. Whether the myocardial inotropic action of endothelin with prolongation of action potential, as well as the presence of endothelin receptors on the cardiomyocytes of the heart, indicate a similarity between endothelin and endocardin remains to be elucidated. Because the presence of an intact EE has a predominantly positive inotropic action, which is prevented by impairment of normal EE function, it could be expected that MCF activity is more prominent than MRF activity. This hypothesis is endorsed by the finding that baseline EDRF activity appeared to be low in isolated cardiac muscle.

The physiologic roles of both MCF (endocardin and, possibly, other substances) and MRF (EDRF-like substance, prostacyclin, and, possibly, other substances) are, as yet, speculative, and further research is needed to reveal their exact nature and mechanisms of action. Until now, it was unknown how the two proposed mechanisms—an electrochemical barrier and the release of a chemical messenger—could, either alone or in concert, participate in a chain of events eventually leading to changes of the contractile proteins to calcium.

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Implications for Cardiac Physiology and Pathophysiology

Although, in man, there still is no supporting evidence, the current experimental studies indicate a role of EE in cardiac physiology and pathophysiology. It may be asked, however, whether the magnitude of EE modulation of myocardial function is important enough to have a substantial implication for cardiac physiology and pathophysiology. Reported in vivo effects of impairment of EE function mention a decrease in left ventricular ejection duration ranging from 3.5 to 9.5%, depending on the experimental conditions. When the effects of EE damage were evaluated by effects on ventricular output and stroke volume, decreases up to 19% were found.# These data demonstrated that modulation of ventricular performance by intact EE function did indeed constitute, both qualitatively and quantitatively, an important regulator of myocardial function; or, alternatively, that the absence of an intact EE may have important implications for normal cardiac function.

Myocardial function depends on cardiac and extracardiac regulatory mechanisms. Cardiac regulatory mechanisms include regulation by Starlings' law and regulation by intact EE. Regulation by Starlings' law involves increased peak performance with prolongation of contraction duration and an increase in contraction velocity. Increased peak performance by the presence of an intact EE, on the other hand, involves, primarily, an increase in contraction duration with only little change in contraction velocity. Both cardiac regulators of myocardial function interact in such a way that, when one regulation mechanism becomes maximized, the functional effects of the other mechanism become less important. Myocardial function is also influenced by extracardiac regulatory mechanisms (based on activation of various hormonal systems). The pattern of response of the extracardiac regulatory mechanisms is distinct from the pattern observed with cardiac regulatory mechanisms. Improved myocardial performance by extracardiac regulatory mechanisms primarily involves a marked increase in contraction velocity with a decrease in contraction duration# (fig. 6). This decrease is substantial with an increase in stimulation frequency or administration of isoproterenol, but is less pronounced with the administration of calcium. Experimental observations have demonstrated that EE may, either fully or partially, mediate inotropic actions of several substances involved in the extracardiac regulation of myocardial function. This means that EE is involved in both cardiac regulation of myocardial function, as a direct regulator of performance of underlying myocardium; and in extracardiac regulation of myocardial function, as a mediator of inotropic action of various hormones (e.g., ANF, vasopressin, angiotensin) and pharmacologic agents (phenylephrine; fig. 7).

Recently, it has been demonstrated that coronary vascular endothelium also modulates contractile characteristics of myocardium. These effects were comparable to the myocardial effects of EE. In addition, modulatory effects on myocardium of endocardial and coronary vascular endothelium appeared to be complementary. Ramaciotti et al. demonstrated that coronary effluent apparently contained not only substances that were produced by endothelial cells, but also substances that stimulated secretion by EE cells (preendothelial factors). Interestingly, the relative production by coronary vascular endothelium of the positive and negative inotropic factors depended, at least in part, on oxygen tension and coronary flow. All these results indicate that regulation of myocardial function by endothelium (vascular and endocardial) probably constitutes a complex phenomenon that remains to be definitively elucidated. Other issues that remain to be resolved are whether interaction between endothelium and myocardium also involves a regulation of endothelial function by myocardially released factors, and whether EE also releases, in the heart cavities, factors that may influence pulmonary and systemic circulation.

In the course of evolving myocardial dysfunction, several compensatory mechanisms are elicited. These include cardiac compensatory mechanisms (e.g., dilatation of the ventricle and cardiac hypertrophy) and extracardiac compensatory mechanisms (based on activation of various hormonal systems). The response pattern of ventricular performance to that volume loading and, finally, overloading appears similar to the response pattern observed with myocardial hypertrophy. Whether this resemblance between the adaptation of myocardial performance through Starlings' law, volume overloading, and myocardial hypertrophy also indicates an interaction with regulation by EE in pathologic conditions is unknown.

In conditions of cardiac dysfunction, plasma levels of several hormones are elevated. These include vasoconstrictive hormones, such as catecholamines.

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Fig. 6. Comparison of the effects of different regulators of myocardial function on left ventricular pressure tracing. Baseline conditions (solid lines) are compared with the tracings obtained after increasing volume, in the presence of an intact endocardial endothelium (EE), and after administration of calcium. Improving myocardial performance by increasing volume, or by the presence of an intact EE, primarily involves an increase in ejection duration. Improving myocardial performance by changing inotropic state by, for example, calcium involves, primarily, an increase in contraction velocity with minor changes in contraction duration.

renin-angiotensin,\textsuperscript{60,61} and vasopressin,\textsuperscript{62} but also vasorelaxing substances, such as ANF.\textsuperscript{63} In addition to their vasoactive effects, these substances often induce either contracting or relaxing effects on the myocardium. For several of these substances, the myocardial effect has been shown to be mediated through intact functional EE. To what extent the role of EE in the responsiveness of myocardium to these various circulating hormones is altered in different pathologic conditions is unknown, but it can be expected that damage to the endocardium with failure of EE to fulfill its functions may have serious consequences.

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Endocardial lesions have been described in a number of pathologic conditions. These include various forms of parietal endocarditis (hypereosinophilic endomyocardial fibrosis and endocardial fibroelastosis). Endocardial endothelium is altered in the presence of mural thrombi after myocardial infarction, in ventricular aneurysms, and in dilated cardiomyopathy. With advancing age, endocardial changes have been reported. Catecholamine-induced endocardial and subendocardial injuries have also been described.

Selective destruction of EE was demonstrated after experimental congestive cardiac failure, after in vitro exposure of cardiac muscle to eosinophils from patients with Löffler's syndrome, and after exposure to high concentrations of serotonin. Because, until a few years ago, no functional role had been attributed to EE, a possible role of EE in cardiac pathophysiology has not been considered. Therefore, further evidence on both morphologic and functional damage to EE in various cardiopathies is necessary to clearly elucidate the role of EE in different pathologic conditions, and to determine whether: (1) regional or generalized dysfunction of EE exists in vivo, and (2) this dysfunction is secondary to the evolution of diseased underlying myocardium, or, instead, morphologic or functional damage of EE may constitute a primary cause of cardiac disease. However, it should be mentioned that all these hypothesized roles of EE in myocardial function do not imply that EE is, necessarily, involved in all physiologic and pathophysiologic processes. For instance, it has recently been shown that cytokines have negative inotropic effects on myocardial muscle. These effects have been attributed to enhanced activity of a constitutive NO synthase enzyme in the myocardium. Removal of EE did not alter these responses, indicating that this phenomenon occurred independently from EE.

Conclusion

Vascular endothelium regulates performance of subjacent smooth muscle, and plays a substantial role in many pathologic conditions. In addition, vascular effects of various pharmacologic agents, including anesthetic agents, appear to be mediated, at least in part, through endothelium. Growing in vitro and in vivo experimental evidence has demonstrated that EE, similarly to the vascular endothelium, regulates performance of underlying muscular structure, i.e., the myocardium, and that it mediates inotropic effects of different circulating elements in the blood. Endocardial endothelium may regulate the function of the subjacent myocardium, possibly by maintaining an electrochemical gradient, by the production and release of active substances (myocardial relaxing and contracting factors) or by a combination of both mechanisms.

The in vivo results permit us to extend the concept of endocardial modulation of myocardial function obtained in vitro to human physiology and pathophysiology. This may introduce an additional approach in the study of cardiac pathophysiology. The field of endocardial physiology and pathophysiology is just opening up, and, until now, only a few questions have been addressed. Future research should be directed toward the elucidation of the many remaining questions with regard to endocardial endothelial function. First, the importance and extent of endocardial damage in different cardiopathies should be carefully reexamined in view of the functional repercussion that it may have.

This discussion highlights the need to direct attention toward the preservation of intact endothelial endocardial function as an important part in improving postoperative cardiac function after cardiac surgery. This question not only involves the problem of cardiac preservation for transplantation, but, also, the problem of cardioprotection during cardiac surgery. Second, available knowledge on EE function presents a very incomplete picture of endocardial regulation of myocardial function. We know that EE interacts with other regulators of myocardial function and mediates the myocardial effects of a number of pharmacologic agents. The physiologic and pharmacologic extent of EE modulation, and its interaction with other control mechanisms, remains to be elucidated. In view of the role of calcium homeostasis in the proposed underlying mechanism of endocardial modulation of myocardial function, the interaction with several drugs interfering with calcium homeostasis is of particular interest. This has its implications far beyond basic cardiac physiology or clinical cardiology. For example, a number of currently used intravenous and volatile anesthetic drugs exert negative inotropic effects through changes in intracellular calcium homeostasis. In view of the large number of patients with cardiac disease presenting for surgery and anesthesia, it would be of interest to evaluate whether any of these drugs has a deleterious effect in the presence of damaged EE. Resolving this question requires, first, a definitive elucidation of the mechanisms underlying modulation of myocardial function by EE. This means isolation and identification of the
now hypothesized myocardial relaxing and contracting factors and, subsequently, elucidation of the mechanisms by which these factors regulate myocardial function, and how these mechanisms interact with the other regulators of myocardial function.

From the above, it is clear that the current knowledge only constitutes a beginning of the elucidation of the in vivo role of the EE. Further clarification and elucidation of the concept of endocardial modulation of myocardial function will require additional experimental research at different levels: in vivo, on isolated cardiac muscles, and on cultured endothelial cells, but, also, at the subcellular and molecular level. Finally, clinical evaluation will permit application of experimental findings to improve the treatment of human cardiac pathology.

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